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NEUROBLASTOMAS AND GANGLIOCYTOMAS OF THE CENTRAL NERVOUS SYSTEM.

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TUMOURS composed of neuroblasts and ganglion cells form a well-recognized group. Most commonly they are found in the sympathetic nervous system, but they occur in the central nervous system with a frequency sufficient to warrant this study. They are not limited to any particular region of the brain or of the spinal cord, occasionally they are encapsulated and enucleable, but more frequently they are infiltrative and simulate gliomas. We shall review the clinical histories of nine such cases, consider their treatment, and describe the histological appearances of the various tumours. Seven of these were found in the cerebrum, and two in the substance of the spinal cord. The latter have been briefly mentioned in a previous study on intramedullary tumours of the spinal cord [6] and one of those in the brain has been described elsewhere [5] because of its association with diabetes insipidus; to complete our study, they have been described here in detail.

In a recent paper on this type of tumour Courville [4] reviewed the literature up to 1930, and as no further contributions have been brought to our notice it seems unnecessary to repeat his excellent summary. A detailed histological description will be given of the tumour found in

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our first case; the remaining tumours in our collection will be compared with this, and their chief variations elaborated.

Report of Cases.

In Case 1 there was a history of: (1) increasing intracranial tension for five weeks; (2) choked discs, with homonymous hemianopsia and partial loss of sense of position; (3) enucleation of neuroblastoma of left temporo-parietal area; (4) six years later, partial removal of recurring tumour, now gangliocytoma; and (5) death after four months.

Case 1.—A girl, aged 16, was brought to the Mayo Clinic on July 16, 1925, chiefly because of headaches. Five weeks previously she had begun to have severe bilateral fronto-occipital headaches early in the morning. About the same time she noticed that she saw double on looking to the right or left, and that she tended to bump into objects on her right. Three days previously she was found in a generalized convulsion.

The patient was well developed and well nourished, but her intelligence and co-operation were poor. The ocular movements were not restricted; horizontal nystagmus to both sides was easily elicited. The pupils were equal, dilated, and reacted sluggishly to light and in convergence. There was acute bilateral choking of the optic discs, measuring 5 diopters, and many hæmorrhages and patches of exudate were present in the retinæ of both eyes. Perimetric fields showed right homonymous hemianopsia. The neck was a little stiff. Moderate loss of the sense of position could be demonstrated in the right index finger and right great toe, and there was some inco-ordination of both the right arm and the right leg. When the patient walked slight ataxia was apparent in the right leg.

At operation on July 24, 1925, a tumour was found involving both the left temporal and left parietal lobes. It was approximately spherical and measured 3 cm. in diameter. In its interior was a cavity containing about 20 c.c. of yellow gelatinous fluid, which coagulated on standing. The growth involved the cortex, and was easily enucleated. Convalescence was uneventful, and the girl returned to her home a month later.

On May 20, 1926, the patient returned for re-examination. Vision was $\frac{6}{6}$ in both eyes. The pupils, pupillary reflexes, and ocular movements were normal. The optic discs showed the pallor of secondary optic atrophy. The homonymous hemianopsia had been replaced by bilateral cæcocentral scotomata. Neurological examination revealed no other changes.

According to a letter dated September 19, 1930, the patient was normal except that her vision was still impaired. She returned to the Clinic on March 5, 1931, complaining of bulging under the cranial scar, and of generalized muscular pain.[1] On March 12 an incision was made into the scalp through

[1] This may have been due to spinal metastases. See recent paper by Cairns and Russell [3].

the posterior limb of the original wound. A pulpy, granular tumour prolapsed: part of this was removed. After the patient returned to her home she was better for three months, but on July 5, 1931, she suddenly became comatose, and died four days later.

Microscopical examination (figs. 1 and 2)—The tumour removed in 1925 was markedly different from that removed six years later. The differences are best crystallized by comparing the stroma and the cells of one tumour with those of the other.

The stroma of the tumour removed in 1925 contained very little adult or hyaline connective tissue, but fibroblasts were numerous, especially toward the edge of the tumour and in the adjacent cerebral tissue, where many astrocytes and some spongioblasts were also to be found. In one part of the surrounding brain small masses of calcium were present, precipitated especially in the walls of arterioles, frequently on astrocytes, and occasionally on ganglion cells; in this area there was an excessive number of fibrous astrocytes. In the interior of the tumour only a few microglial cells, an occasional scavenger cell, and a number of diffusely arranged lymphocytes were present. The walls of the blood-vessels were thickened by proliferation of endothelium, which was occasionally sufficient to occlude the lumen; associated with these occluded vessels were many areas of necrosis surrounded by polymorphonuclear leucocytes. Occasionally the perivascular connective tissue was also increased; vessels so affected resembled those found in any spongioblastoma multiforme.

The stroma of the tumour removed in 1931 contained an abundance of connective tissue; some of its heavier bundles had undergone hyaline degeneration; although for the most part adult in type, this tissue was loose in texture. A certain amount of less mature connective tissue was also present; this contained well-differentiated fibroblasts. These did not stain bright red with the fuchsin of van Gieson's stain; compared with the cells of adult connective tissue, their nuclei were larger, more oval, and contained more chromatin, and their fibrils were shorter and heavier. The walls of the blood-vessels were normal; in many perivascular spaces lymphocytes were present, sometimes to excess. Lymphocytes were also found both diffusely throughout the tumour and occasionally collected in islands.

Most of the cells of the 1925 tumour were round or oval, a few were bipolar, and an occasional larger cell was polygonal. The dendrites arising from these cells were short and rudimentary. Only the polygonal cells contained Nissl substance, which was arranged in very fine granules around the periphery of the cell, and in its dendrites. In spite of the absence of Nissl substance from the smaller cells, the common origin from neurogenic tissue of all the cells of the growth was clearly indicated by their affinity for silver, and by the configuration of their nuclei. These were large, round and vesicular, and each contained a central deeply staining nucleolus. They were unusually eccentric, and lay close to the wall of the cell, or at one end of the unipolar and bipolar cells. Rarely one cell contained two nuclei, but never more than two; mitotic figures were numerous. The cells were readily impregnated with silver;

those axones which were so stained did not arise from the cells of the tumour, but from cerebral cells which had been included by its invasion.

The cells of the 1931 tumour, though not numerous, could be demonstrated by the toluidine blue stain in all parts of the growth. They had a tendency to grow in groups surrounded by connective tissue, but many single cells could be found. Most of the cells had fairly distinct outlines. They had three, four, or five sides, with a corresponding number of dendrites. The latter varied in size; the majority were relatively short and had broad bases, but occasionally larger dendrites were present. Some bipolar cells were to be found; these had heavy processes, tapering from both ends into the surrounding tissue. The cytoplasm of the cells was abundant, and frequently contained small vacuoles. It did not stain uniformly; many deeply staining chromatin granules were present, arranged diffusely throughout the cytoplasm and in the dendrites. In certain cells these granules were larger and more prominent, and were collected beneath the boundary of the cell; in these cells fine tigroid granules were present around the nucleus. Mitotic figures were absent. Sections impregnated with silver confirmed the appearances seen in those stained with toluidine blue; the characteristic nuclei were well demonstrated. Usually they were central in position; occasionally they were eccentric, and lay close to the cell boundary, but without causing any bulging of this.

The 1925 tumour was classified as a neuroblastoma; the 1931 tumour as a gangliocytoma.

In Case 2 there was a history of visual hallucinations, and progressive hemiplegia and aphasia for one year. Homonymous hemianopsia was present. Generalized convulsions, increasing weakness, coma and death resulted. Necropsy revealed a gangliocytoma of the left temporal lobe.

Case 2.—A man, aged 53, was brought to the Clinic on November 27, 1919, because of increasing weakness of the right half of the body, and of difficulty in expressing himself. One year previously a "red ball" suddenly appeared before the patient's right eye; he fell, and was unable to rise for ten minutes. Similar, although milder, seizures recurred a month later, and at irregular intervals thereafter. Four months previously the right leg began to drag, and this disability gradually became more marked. Two months previously the right hand became numb, stiff and slow. Four days before his arrival the right-sided weakness increased rapidly. One month previously he began to have increasing difficulty in expressing his ideas in words.

The blood-pressure in millimetres of mercury was 106 systolic and 75 diastolic. Visual acuity was 6/10 in both eyes. The pupils were equal, and reacted promptly to light and in convergence. Ophthalmoscopic appearances were normal. Almost complete right homonymous hemianopsia was present. The patient was markedly aphasic, and hemiplegia was almost total on the right side. Cerebrospinal fluid obtained by lumbar puncture was clear and colourless, but under increased pressure. On the day following the lumbar

puncture the hemiplegia was found to be complete; on the same evening the patient became comatose and died.

Necropsy.—The brain presented the usual signs of increase in intracranial pressure. Occupying chiefly the left temporal lobe was a tumour 4 cm. in diameter, poorly demarcated from the surrounding brain. The growth extended upward into the adjacent part of the parietal lobe and mesially into the cerebral peduncle; it compressed and lengthened the part of the left optic tract posterior to the chiasm. Much of its substance was necrotic and consisted of hæmorrhagic gelatinous débris. The lateral ventricles were not dilated, nor did the growth invade the left ventricle.

Microscopical examination (fig. 3).—The stroma of the growth was sparse and œdematous. The blood-vessels were well formed; endothelial proliferation was absent. Occasionally lymphocytes were found, but only in the perivascular spaces. The tumour was cellular; the cells varied much in size, and had a tendency to grow in groups rather than diffusely. Stained by toluidine blue, the majority appeared pyramidal or polygonal in outline, but many bipolar and unipolar cells were also present. In the pyramidal and polygonal cells the cytoplasm was more abundant, and occasionally vacuolated. Fine tigroid granules were present in the cytoplasm, and in some cases they had collected beneath the cell-boundary into larger masses; the few dendrites which were present contained a similar finely granular substance. The dendrites were not so sharply demarcated as in normal adult cells, but had broad bases, and short and indefinite outlines. The bipolar and unipolar cells stained a more uniform pale blue, and had few granules in their cytoplasm. The cells of the tumour had an affinity for silver, which outlined their bodies and dendrites; axis-cylinders were not observed. All the cells of the growth had characteristic nuclei; these were large, round and vesicular, and contained little chromatin except a prominent deeply-staining nucleolus. They were large in comparison with the size of the cell, and usually were situated in the middle of the cell-body, although occasionally they were eccentric. Cells more immature than the bipolar stage of neuroblasts were not identified and mitotic figures were absent.

This tumour was classified as gangliocytoma.

The history in Case 3 was of mental deterioration for six months: acute exacerbation of increase in intracranial pressure, coma and death. At necropsy a gangliocytoma of the left frontal lobe was found.

Case 3.—A physician, aged 39, was brought to the Clinic on July 6, 1920, in a semi-stuporous condition. Six months previously he began to lose interest in his professional work and in his home life, and three months later his condition progressed to drowsiness, and considerable stupor for the greater part of the time. Three weeks previously he began to have left-sided supra-orbital headaches, which occasionally radiated to the occiput and were associated with diplopia. Two weeks previously projectile vomiting appeared, and at the same time his speech became confused.

The patient was only semiconscious and much reduced physically. The blood-pressure was 132 systolic and 80 diastolic; the pulse-rate [42] was consistently slow. The pupils were equal in size, and reacted to light and in convergence. Both optic discs were swollen, the right to a height of 1 diopter, the left to 2 diopters. It was thought that the patient's general condition was too poor for even decompression to be considered; the following day he died.

Necropsy.—The brain was dry, and its convolutions were greatly flattened. The left frontal lobe was larger than the right, the mesial surface of which it indented. Occupying the enlarged lobe was an extensive, poorly defined tumour, the central part of which was necrotic. Macroscopically the tumour extended from the tip of the frontal lobe to the frontal operculum and to the posterior ends of the superior and middle frontal convolutions.

Microscopical examination (fig. 4).—Little stroma was present; the tumour was highly cellular. The walls of the blood-vessels were thin, and showed endothelial proliferation with mitosis; frequently the proliferation had led to obstruction of the lumen, and so to the formation of areas of necrosis. Lymphocytes and polymorphonuclear leucocytes were abundant around these areas, and the former were numerous around the blood-vessels.

On the whole, the cells of the tumour grew diffusely, although occasionally they were collected into clusters; they varied greatly in size. The majority were polygonal, and contained finely granular Nissl substance. In spite of the preponderance of adult cells, mitotic figures were numerous in less differentiated cells. The cells had an affinity for silver, which outlined their bodies and dendrites; axis cylinders arising from the cells of the tumour could not be demonstrated. The nuclei were characteristically large and vesicular, and contained central deeply staining nucleoli. Most of the nuclei were eccentric and lay under the cell membrane; many of these were oval. Some cells were swollen; the central part of these stained lightly with toluidine blue, and the periphery contained definite Nissl granules; in such cells eccentric nuclei were commonly found. It was impossible to demonstrate spongioblasts or astrocytes in the depth of the growth, but at its margin normal and degenerating astrocytes were identified.

This tumour was classified as a gangliocytoma containing many neuroblasts.

The history in Case 4 was of progressive loss of vision, diabetes insipidus, and hypopituitarism for two years. The region of the chiasm was explored, following which the patient died. Necropsy disclosed a gangliocytoma of the third ventricle.

Case 4.—A girl, aged 13, was brought to the Clinic on October 10, 1927, because of headache and progressive loss of vision. Two and a half years previously she began to pass large quantities (4 litres in twelve hours) of almost colourless urine which did not contain sugar, and at the same time

she suffered from excessive thirst. A diagnosis was made of diabetes insipidus. This persisted for two years, during which she steadily gained in weight until she weighed twice as much as her normal. Most of the time she was drowsy, but she remained at school and made fairly satisfactory progress. Four months before her examination she began to complain of dimness of vision, which steadily progressed, so that after two months she often collided with people and objects. Two months previously she began to have dull pounding right frontal headaches; these occurred daily. About the same time she began to lose weight, and thereafter she was subject to occasional attacks of weakness, during which she perspired profusely. For several days before her arrival she was very weak, and spoke in a peculiar slurring manner.

The girl was well developed and well nourished, being 142 cm. tall and weighing 43·1 kg. The blood-pressure was 98 systolic and 64 diastolic. The patient slept in a drowsy stupor most of the time, but occasionally complained of pain over the right eye; nausea accompanied the pain, and sometimes she vomited. She was able to see large objects, but was unable to read even the largest print. The left pupil was somewhat larger than the right; both reacted promptly to light and in accommodation. The optic discs were full and pale. Perimetric examination disclosed right homonymous hemianopsia. In other respects, neurological examination was negative. In roentgenograms of the head the sella turcica appeared to be normal. There was no serological evidence of syphilis.

At operation the region of the optic chiasm was approached by elevating the left temporosphenoidal lobe. Evidence of a tumour in or about the chiasm was not detected. The patient withstood the operation poorly, and died twelve hours afterwards.

Necropsy (fig. 5).—The exterior of the brain did not show any sign of increase in intracranial pressure. A tumour was found in the lower and anterior part of the floor of the third ventricle, destroying the tuber cinereum and corpora mammillaria. The growth compressed lightly the infundibulum and hypophysis, but did not invade either. Anterior to the infundibulum the tumour had transgressed the floor of the third ventricle to invade the optic chiasm and posterior parts of the optic nerves; tumour tissue was also found in both optic tracts, especially in the left. The lateral walls of the third ventricle were little involved. The anterior part of the tumour had extended between the frontal lobes, without invading either. The growth as a whole had not interfered with the flow of cerebrospinal fluid. It was not sharply demarcated from the surrounding brain; it contained several small cysts, and a larger one anterior to the left optic thalamus.

Microscopical examination.—Sections of the optic chiasm stained by Weigert's myelin sheath method showed that much of its structure had been destroyed by tumour cells, so that myelin sheaths were absent. Tumour tissue could not be found in sections of the infundibulum and of the hypophysis. In the growth itself many lymphocytes and plasma cells were present, especially in the areas of cystic degeneration. The majority of the blood-vessels had thin

walls, the lining endothelium of which was proliferating and even contained mitotic figures. Throughout the tumour only a few astrocytes were found, but there were many in the adjacent brain tissue. The predominating tumour cells were of a type intermediate between neuroblast and ganglioeyte ; some of these were round cells without processes ; others had one, two, or several processes. In many such cells mitotic figures were present. Almost mature ganglion cells were also to be seen, these had varying numbers of processes and contained immature Nissl granules. All the cells of the growth had the characteristic large, round, vesicular nucleus, with its central deeply staining nucleolus ; cells containing two or more such nuclei were uncommon.

This tumour was classified as a gangliocytoma containing many neuroblasts.

The history in Case 5 was of loss of vision and progressive signs of internal hydrocephalus for six months. Ventricular estimation and ventriculography were carried out. The patient died following operation. Necropsy revealed a gangliocytoma of the third ventricle.

Case 5.—A man, aged 23, was brought to the clinic on March 18, 1931, because of loss of vision. Six months previously vision in the right eye had failed suddenly, and one month later that of his left eye also had failed. Four months previously he began to have headaches in the frontal region, and two months later these began to be associated with projectile vomiting. Two weeks previously he complained of abnormal sensations in the left hand, and evidence of blunting of intellectual and emotional faculties appeared.

The patient was well developed and well nourished. His co-operation was so poor that examination was difficult. The right pupil was larger than the left, and its reflex to direct light was markedly diminished. Ophthalmoscopic examination showed acute choking of both optic discs to a height of three diopters, with retinal hæmorrhages and exudates. Apparently he was blind in his right eye, but perimetric fields could not be obtained. Stereoscopic roentgenograms of the skull revealed convolutional atrophy of its inner table, and erosion of the sella turcica. A rapid, fine tremor of both hands, of both static and kinetic types, was present. Three days after his admission to hospital he had a generalized convulsion. A diagnosis was made of internal hydrocephalus, due to unlocalized tumour.

On March 24, 1930, ventriculography was performed. Ventricular punctures revealed bilateral hydrocephalus. The ventriculograms indicated that the lesion was a tumour involving the third ventricle. On the second post-operative day the patient died suddenly of respiratory failure.

Necropsy (fig. 6).—Signs of extreme increase in intracranial pressure were marked. The brain was dry and its convolutions were flattened. Numerous dural herniations were present, especially on the floor of the middle fossæ. The uncinate gyri, the gyri recti and the olfactory tracts were grooved as a result of pressure on the edges of the tentorium and on the clinoid processes. Both lateral ventricles were considerably dilated. In the lower half of the

anterior horn of the left lateral ventricle was found a greyish, cystic, hæmorrhagic tumour. Mesially this was attached to the left side of the septum pellucidum, anteriorly it extended into the head of the left caudate nucleus, and posteriorly it invaded the left optic thalamus. A small part of the growth eroded the septum pellucidum and appeared in the right lateral ventricle. The posterior part of the tumour occluded the left foramen of Monro, and displaced the septum pellucidum to the right so as to occlude the right foramen of Monro. On the lateral wall of the anterior horn of the right lateral ventricle was a small grey nodule, 5 mm. in diameter, which had an appearance and consistence similar to that of the main mass of tumour.

Microscopical examination (fig. 7).—The main tumour was highly cellular, although its blood-vessels had well-formed normal walls. Little stroma was to be seen, and astroblasts, astrocytes and spongioblasts were absent. The cells of the tumour were unusual in that they had some of the characteristics of astroblasts: large, homogeneous, eosin-stained cell bodies and eccentric nuclei. Stained with toluidine blue, the cytoplasm of certain of the cells was almost homogeneous, especially in the middle: in some cells small Nissl granules were collected around the periphery, in others small granules were scattered diffusely throughout their cytoplasm, and large granules were collected around the periphery. In sections impregnated with silver few cell processes could be identified, but often one end of a cell displayed an indistinct frayed outline like a fish's tail: axis-cylinders could not be demonstrated. The nuclei were typical: they were large, round, and vesicular, and each contained a deeply staining central nucleolus. Multinucleated cells were not observed.

This tumour was classified as a gangliocytoma. The small tumour on the lateral wall of the right lateral ventricle was an astroblastoma (fig. 8).

The history in Case 6 was of generalized convulsions and change in personality for eighteen months. A parasagittal gangliocytoma was removed, and the patient recovered.

Case 6.—A woman, aged 36, came to the clinic on August 27, 1927, because of attacks of generalized convulsions and failure of vision. Eighteen months previously she had had a sudden generalized convulsion which lasted for two to three minutes. After recovering from this she was dazed and went to bed: during the same day she had two similar attacks. After these convulsions a persistent weakness of the muscles of the left side of the face was noted. A week later she returned to work. Thirteen months previously she had another convulsive attack, which was followed by a feeling of weakness so marked that she stopped work: three months later she had another convulsion. Six months previously she began to have dull bitemporal headaches once a week. Each headache lasted one to three hours, and they persisted for three months, when they were replaced by severe stabbing pain in the temples and eyeballs. At this time the patient had a good deal of nausea, but practically never vomited. Three months previously her vision

began to fail and she had occasional diplopia. After her first convulsion a change in personality appeared: she became irritable, lost interest in her household and wanted to stay at home to be left alone.

Vision in the right eye was $\frac{6}{6}$ and in the left eye $\frac{6}{7}$. Both optic discs were swollen to 4 diopters. Perimetric fields showed concentric contraction for form and for colours, with enlargement of both blind spots. Weakness of the left side of the face was present. The tendon reflexes were more active on the left side of the body, but the left plantar reflex was flexor in type. A roentgenogram of the skull revealed, in the right frontal area, enlarged channels for diploic veins. A diagnosis was made of tumour involving the right frontal lobe.

On September 7, 1927, this region was explored. A tumour was found attached to the dura mater over the middle frontal convolution. It was smooth, round and indented the brain without invading it. Because of loss of blood from the large sinuses in the bone, the operation was divided into two stages. Nine days later the wound was reopened and a second bone flap turned down to the left side across the superior longitudinal sinus. The growth, which measured 15 by 18 cm., invaded the longitudinal sinus and appeared on the left side as a mass measuring 3 to 2 cm. It appeared to be encapsulated, and was, so far as could be determined, completely removed.

The patient had an uneventful convalescence. She was examined again in January, 1929, when she was in good physical condition. The only remaining sign of her illness was secondary optic atrophy: this had given rise to inferior nasal hemianopsia in the left eye, and inferior altitudinal hemianopsia in the right eye. Toward the end of July, 1929, she returned because she had had a convulsion. For some time her memory had been impaired, and occasionally her mind wandered. Further operation was not advised.

Microscopical examination (figs. 9 and 10).—The growth was similar to that found in Case 5. The blood-vessels had well-formed normal walls, and there were no extensive areas of necrosis. Lymphocytes were absent, and only around the blood-vessels was any connective tissue demonstrable. The tumour cells were large. They contained finely granular Nissl substance, which was often collected into larger granules under the cell membrane. No well-formed dendrites were present, although each cell had a frayed termination at one end. The nuclei were characteristically large, round and vesicular, and contained deeply staining nucleoli which were often eccentric; occasionally giant nuclei containing two nucleoli were present. Binucleated cells were common, and occasionally multinucleated cells were observed, but mitotic figures were absent. The silver stain did not impregnate any axis-cylinders. Some of the cells of the growth were undergoing cystic degeneration, so that many small cavities outlined by a delicate membrane were present throughout the tumour. Most of these cysts were empty, but a few contained homogeneous material which stained with both eosin and toluidine blue. The stages in the formation of these cysts from swollen degenerating tumour cells could be followed. Cysts of this type are almost always present in gangliocytomas arising from

the sympathetic nervous system, but this tumour was the only one in our series in which their occurrence was observed.

The tumour was classified as a gangliocytoma.

In Case 7 the history was of increasing intracranial pressure for five months, and homonymous hemianopsia and hemiparesis. A gangliocytoma of the right parietal lobe was partially removed.

Case 7.—A woman, aged 39, came to the Clinic on July 13, 1931, complaining of headaches and drowsiness. Five months previously she began to complain of occasional aches in the right fronto-temporal region; these gradually became more frequent and more severe, until after two months they occurred daily, for periods of three to twelve hours. Following this the headaches became more moderate; their evolution was always fairly constant; first a feeling of "coldness" was noted over the right fronto-temporal region, then dull pain and lastly sharp pain. The most severe headaches were associated with giddiness. Three months previously, when the headaches were at their worst, the patient became so drowsy that she slept most of the time and was unable to do her housework: at times it was impossible to rouse her. After two months she became less sleepy. Two weeks before her examination she complained of general weakness and of difficulty in walking.

The patient was well developed and well nourished. Vision was $\frac{6}{7}$ in both eyes. The pupils, pupillary reflexes and fundi were normal. Perimetric fields disclosed complete left homonymous hemianopsia. There was no roentgenological evidence of intracranial disease. Neurological examination disclosed moderate weakness of the whole left side, with a corresponding diminution of speed of movement and exaggeration of the deep reflexes. On the left side the superficial abdominal reflexes were diminished and the great toe responded by extension to stimulation of the sole of the foot. Sense of position was moderately decreased in the left index finger and markedly reduced in the left great toe. Some inco-ordination of the left arm and left leg could also be demonstrated. A diagnosis was made of tumour of the right parietal lobe.

At operation the convolutions in this area were found to be of a firm, rubbery consistence. The tumour, which extended deeply into the white matter, was partly extirpated with the electro-surgical unit. The patient made an uneventful recovery.

Microscopical examination (figs. 11, 12, and 13).—The architecture of this tumour was quite different from that of all the others; it was a diffuse growth limited almost entirely to the grey matter, the thickness of which it had greatly increased. Its blood-vessels had normal walls, and lymphocytes were absent. The number of ganglion cells in the cortex was enormously increased. The cells varied in size from small round to large pyramidal; oval cells predominated, but many cells were pyramidal and polygonal cells were also found. The arrangement of the structures forming the cortex was abnormal; the apical dendrones of the pyramidal cells were not, as is usual, directed toward the surface of the convolutions, but passed indiscriminately in any direction. The

axes of the oval cells lay in all directions. The cortical layers described by Brodmann [2] were disorganized, so that it was impossible to distingush them; thus where normal cortex merged into neoplasm layers one and five lost their identity, then layers three and six, whereas layers two and four retained their identity longest. The greatest increase in large cells occurred in layers five and six. However, the most remarkable feature was observed in the subpial layer. Normally this does not contain ganglion cells, but in the tumour there were large numbers of small pyramidal and oval cells immediately beneath and in contact with the pia mater, although more primitive cells from which they could differentiate were not present. The surface of the convolutions was irregular and nodular; the nodules consisted of masses of small ganglion cells. Undoubtedly normal ganglion cells were present in the cortex, but in addition there were many other cells which were abnormal in size, shape and distribution. In sections stained with toluidine blue, every cell was seen to have cytoplasm which stained blue and contained Nissl granules; in the larger cells heavier tigroid granules were abundant and were present in the dendrites also. All these cells had an affinity for silver. Implantation cones were absent, yet axis-cylinders arose from many of the cells. All the cells had characteristic large round, vesicular nuclei, each of which contained a deeply staining central nucleolus. The nuclei were not always situated in the centre of the cell; binucleated cells were present in small numbers; more than two nuclei were not observed in any one cell. There was considerable variation in the ratio of the size of the nucleus of a given cell to the amount of its cytoplasm, but in general the nucleus was large in comparison with the size of cell; in the smaller cells, the nucleus occupied most of the cell body. The cells of the tumour had a tendency to grow in groups or clusters. Many, especially in layer six, showed satellitosis. Throughout the tumour astrocytes were increased in number, but all were of adult type; spongioblasts were absent. At the edge of the growth swollen degenerating astrocytes were found; some of these had two nuclei, and therefore had become "gemästete" cells. In spite of invasion and compression of the grey matter, the axis-cylinders in the underlying white matter did not show any signs of degeneration, such as swelling, beading or fragmentation.

This tumour was classified as a gangliocytoma.

The history in Case 8 was of a progressive lesion in the cervical part of the spinal cord for three years. An intramedullary gangliocytoma was partially removed, with temporary improvement. Death occurred seven months later.

Case 8.—A woman, aged 34, came to the Clinic on May 23, 1921, complaining of pain in the shoulders and loss of function of the arms and legs. Three years previously, when three months pregnant, she began to suffer pain in both shoulders; this came in attacks lasting from two to seven days and recurred several times during a month. After this she had no further

discomfort until after delivery, when the pain reappeared and grew more severe. One year previously the pain began to radiate down the inner side of the left arm to the hand, and to be associated with numbness and tingling of the fingers. A year and a half previously she first observed clumsiness and weakness of the left hand; sixteen months later weakness and numbness first of the left leg and then of the right arm appeared, and after a short interval the right leg became weak. During the three months preceding examination she had repeatedly burned both hands without feeling pain.

The patient held her neck stiffly. In both arms, especially in the left, muscular weakness and atrophy were present, particularly in the small muscles of the hands. Power was diminished in the left leg and tonus increased. Sensibility to touch, pain and temperature was moderately impaired over the upper part of the thorax and more so on the inner aspect of the right forearm. Along the inner aspect of the left forearm sensibility to pain and temperature was markedly impaired, but sensibility to touch was practically normal. Sense of position was much diminished in the toes of the left foot, but normal in the right. Vibrations were not appreciated in either leg. The tendon reflexes were not obtainable in the arms; those of the right leg were normal those of the left leg exaggerated. Babinski's sign was present on both sides. There was a little lack of control of both rectal and vesical sphincters. Cerebrospinal fluid obtained by lumbar puncture was clear and colourless; it contained an excess of protein, and six lymphocytes in each cubic millimetre.

On June 9, 1921, the spines and laminæ from the fifth cervical to the second thoracic vertebræ were removed. The spinal cord was greatly enlarged, its greatest diameter being opposite the seventh cervical vertebra: above and below this point the swelling tapered in a fusiform manner. An incision was made in the right posterior column: at once a soft purplish tumour partly extruded. About four-fifths of the tumour was removed, after which the cord collapsed. Convalescence was uneventful. After returning home, the patient gradually improved during July; however, in the beginning of August she began to fail, and died on January 6, 1922.

Microscopical examination.—The tumour was not very cellular. Its blood-vessels were well formed and their walls were for the most part normal, but in one area excessive hyaline thickening of the tunica media was present, of such a degree as almost to occlude the lumen. However, necrotic areas were not discoverable in this part of the growth. Connective tissue and fibroblasts on the one hand, and astrocytes and spongioblasts on the other, were entirely absent.

Although for the most part diffuse, in certain areas the cells of the tumour had a tendency to collect in groups of from three to twenty. The cells were remarkably uniform in appearance; they were relatively large and usually polygonal in shape, seldom pyramidal or round. Their outline was convex, not concave like that of the normal ganglion cells of the spinal cord. Their margins were not always sharp, but frequently faded into the surrounding tissue; dendrites were not numerous, although most cells had one or two

which were small and indistinct. Fine granular Nissl substance was present in the bodies of the cells and in their dendrites; large granules similar to those found in normal ganglion cells were not seen, nor was pigment, so common in the adult ganglion cells of the anterior horns of the spinal cord, found in any tumour cell. The cells had characteristic nuclei, large, round and vesicular, containing one deeply-staining central nucleolus. Binucleated cells were common, but more than two nuclei were rare and giant cells were not found. No immature forms of ganglion cells could be identified. The cells of the growth had a characteristic affinity for silver.

This tumour was classified as a gangliocytoma.

In Case 9 the history was of a progressive lesion of the cervical part of the spinal cord for four and a half years. Spinal subarachnoid block was demonstrated. An intramedullary gangliocytoma was removed and Roentgen treatment was given. Marked improvement followed.

Case 9.—A woman, aged 27, came to the Clinic on February 5, 1930, complaining of pain in the arms and in the right side of the face and head, and of loss of strength. Four and a half years previously, a few months after the birth of her first child, she began to experience sharp aching pains in the left scapular region. Turning the head increased the pain and caused it to radiate to the left of the neck: however, it was not increased by coughing or sneezing and did not waken the patient at night. Two years previously the pain had spread down the left arm to the hand, especially to the fourth and fifth fingers. One year previously pain appeared in the right side of the face and head: it was sharp and smarting and was associated with flushing of the face; after six months it extended to the right side of the neck and upper part of the thorax. Eighteen months previously the patient noticed loss of power in the left arm, and six months later in the right arm. Three months previously increasing weakness of the legs appeared.

The patient was emaciated. There was moderate flaccid paralysis of both trapezius muscles and of both arms, particularly of the left. Moderate loss of power was noted in both legs. The tendon reflexes were absent in the arms: in the legs they were exaggerated and Babinski's sign was present on both sides: the abdominal reflexes were absent. There was loss of perception of pain and temperature over both arms, and over a band-like zone extending from the second to the fifth rib; above the level of the second rib partial analgesia and thermanæsthesia was determined, including the territory of both trigeminal nerves. Over the lower two-thirds of the trunk, the legs and the anterior aspect of the thighs, partial loss of sensibility to pain and temperature existed; this diminished in intensity from above downward. Sensation was intact over the perineum, buttocks and posterior aspects of the thighs. Vibration was not perceived over the distal ends of the bones of the forearm, and over the right malleoli; over the left malleoli its perception was diminished. Sense of position was lost in the third, fourth, and fifth fingers of both hands,

and somewhat disturbed in the toes of both feet. Cerebrospinal fluid obtained by lumbar puncture was clear and yellowish; its pressure was not altered by compression of the jugular veins. It contained 6 small lymphocytes in each cubic millimetre, and 340 mgm. of protein per 100 c.c. A diagnosis was made of intramedullary tumour.

At operation, the spines and laminæ of the second to sixth cervical vertebræ were removed. The theca did not pulsate. The spinal cord was greatly swollen and soft. When the left posterior column was incised an encapsulated maroon-coloured tumour was exposed: the greater part of this was easily separated from the tissue of the cord and removed. Caudally the growth extended to the eighth cervical segment, where a small piece of tumour which was invading the cord was not disturbed. Cranially the growth reached the first cervical segment. Convalescence was at first stormy, probably on account of œdema of the medulla. However, the patient was able to use her legs and her right arm. Following a transfusion of blood on the third post-operative day she improved rapidly, and was dismissed from our care sixteen days after operation. She has returned at intervals for roentgenotherapy, and has regained her physical well-being. At the present time, two years after operation, there is not any evidence of recurrence of the growth. Some weakness persists in the muscles of the shoulder-girdles and hands, and slight weakness in both legs. However, the tendon reflexes of the arm are present. Babinski's sign is still present on both sides. The return of sensation has been less complete: there is almost complete loss of perception of pain and temperature over both arms, over the thorax above the second rib, and over the territory of the upper cervical nerves. Below the second rib there is decreasing analgesia and thermanæsthesia down to the level of Poupart's ligaments, below which sensation is normal. Sense of position is completely lost in the fingers, but normal in the toes. Vibratory sense is markedly disturbed over the distal ends of the bones of the forearms, and moderately diminished over the malleoli. The gait is slightly spastic. Control of the sphincters is normal.

Microscopical examination (fig. 14).—This tumour was more cellular than that removed in Case 8. The stroma was scanty, stained pale pink with eosin and did not contain any lymphocytes; neither glial cells nor glial nuclei were present. The blood-vessels were well formed. The cells had a tendency to grow in groups; they varied greatly in size and shape, but most were polygonal. Their cytoplasm was scanty and vacuolated, and contained numerous fine Nissl granules which tended to collect in larger masses at the periphery. The cells had a strong affinity for silver. When present, dendrites were relatively short: they contained Nissl granules. Immature and indistinct axis cylinders were present, but poorly impregnated. The nuclei of the cells were characteristically large and vesicular, and each contained one deeply staining central nucleolus. The size of the nuclei relative to the bodies of the cells was much greater than in normal cells. Usually the nucleus was central; binucleated cells were rare, and more than two nuclei were not seen in any one cell. Only a very few bipolar and unipolar neuroblasts were identified.

The tumour was classified as a gangliocytoma.

Comment.

It would be unprofitable to enter into a lengthy criticism of the merits of the various terms which have been applied to tumours containing ganglion cells or neuroblasts; it is undoubtedly true that each author has a good reason or reasons for the term that he uses, and for the most part it is applicable to the tumour he is describing. In our series there are marked variations in the type and in the distribution of the neoplastic cells, and also in the type of supporting structures, so that a descriptive term applicable to one tumour would be unsuited to the others. Our suggestion that the term "neuroblastoma" be applied to tumours containing neuroblasts or primitive nerve-cells, and the term "gangliocytoma" to tumours containing adult nerve-cells, is an attempt to bring the nomenclature of this group of neoplasms into line with that of the gliomas. In one of our cases hyaline connective tissue formed the stroma and made up more than one half of the neoplasm; in another more astrocytes were present than normally; in another some fibroblasts were present, and in still another no stroma of any kind could be demonstrated. Because of these variations in the type of stroma, we have found it impracticable to apply a term which would describe the stroma of each neoplasm as well as the degree of differentiation of the tumour cells themselves, just as pathologists have found it necessary to omit the connective tissue stroma from the names of carcinomas of various organs. As in the gliomas, there was considerable variation in the types of cell which were present in our series of tumours. There was a greater tendency for the cells found in a given tumour to be more uniform in their stage of differentiation than is usually the case in a glioma, although we have described several tumours in each of which several stages of differentiation were present.

The most interesting feature of Case 1 is the fact that the tumour recurred after an interval of six years, and that although both tumours were neurogenic in type, the first was cellular, the majority of the cells being neuroblasts with little cytoplasm and without dendrites or axis cylinders; whereas the second tumour was comparatively acellular, such cells as were present being well differentiated ganglion cells with well-formed dendrites, abundant cytoplasm and Nissl granules. In spite of this difference in the cellularity of the neoplasms, and in the degree of differentiation of the cells themselves, both types of cells had an affinity for silver, and in both nuclei of the same type were present. These were characteristic not only of these two tumours, but of the entire group; they were large, round and vesicular, and contained little

chromatin except one prominent central deeply-staining nucleolus. In the study of neoplasia in general, it is unusual to find that a tumour made up of primitive cells, which has been partially or even almost completely extirpated, should recur after a period of years as a more completely differentiated growth ; usually the cells of a recurring tumour are more primitive than those of the original growth. In the more active neoplasm the sparse stroma was younger but less abundant than that of the more highly differentiated tumour, whose stroma contained much hyalinized connective tissue. The structure of their blood-vessels corresponded to the rapidity of growth of each tumour. Both these tumours were infiltrative, thus simulating the macroscopic appearance of most of the gliomas.

In Case 2 the majority of the cells were well differentiated ganglion cells of pyramidal or polygonal shape, but in addition there were some more immature neuroblasts belonging to the unipolar and bipolar stages of differentiation. In spite of the presence of the latter cells the tumour was classified as a gangliocytoma, because mature ganglion cells were dominant. Some of these cells showed slight vacuolization of the cytoplasm, but this had not progressed to the stage of cyst formation so common in gangliocytomas of the sympathetic nervous system. As in our first case the cells had an affinity for silver. Their nuclei were characteristic, and showed deeply staining central nucleoli, as did the nuclei of the neuroblasts also. As in the majority of gangliocytomas, the cells of this tumour had a tendency to grow in groups or small clusters rather than diffusely.

The tumour in Case 3 was classified as a gangliocytoma, in spite of the fact that neuroblasts were present and that mitotic figures were seen. The majority of the cells were well differentiated ganglion cells, which co-existed in some areas with more primitive cells. At least parts of this tumour were growing rapidly, a feature reflected by endothelial proliferation in thin-walled blood-vessels and by areas of necrosis. These necrotic areas explain the presence of the large cysts so commonly seen in gangliocytomas of the brain, and also of the polymorphonuclear leucocytes which were present only in necrotic tissue. Lymphocytes were present everywhere in this tumour ; in places they were collected into islands, a common picture in cerebral gangliocytomas. There was little stroma other than the blood-vessels, but near and around the edge of the growth adult astrocytes and some degenerating forms were seen ; these did not seem to be growing with the ganglion cells or neuroblasts. In the same areas of the tumour

axis-cylinders derived from invaded brain tissue were present, but it was impossible to demonstrate axis-cylinders arising from the cells of the growth.

Few comments are necessary on Case 4 of this series, as it has been described at length elsewhere [5]. It was classified as a gangliocytoma containing large numbers of neuroblasts; the better differentiated cells predominated only slightly. The situation of this tumour and the associated clinical symptoms were most interesting. In spite of the fact that the patient suffered from evident hypopituitarism, the hypophysis was only slightly compressed, and neither it nor the infundibulum was invaded by the tumour.

In Case 5 the cells of the tumour were quite different from those in any of the first four cases. They were remarkably uniform throughout and simulated astroblasts by possessing abundant homogenous eosin-staining cytoplasm, but there the resemblance ended. These cells had no vascular processes or any affinity for the gold of Cajal's gold chloride and sublimate method. They did have an affinity for silver, and Nissl granules were present, although small and immature and collected especially at the periphery. No well-differentiated adult ganglion cells with dendrites or axis-cylinders were present. The nuclei and nucleoli were characteristic. Stroma was sparse; astroblasts, astrocytes, and spongioblasts were absent, and there was little connective tissue in the neoplasm except around the blood-vessels; lymphocytes were not present. In short, the most interesting features of this tumour were the uniformity of the cells and the complete absence of primitive neuroblasts and mitotic figures.

In Case 6 the tumour cells closely simulated those of Case 5; other points of resemblance were the absence of stroma, the structure of the blood-vessels, the slight amount of connective tissue and the absence of lymphocytes. Primitive tumour cells and necrotic areas were absent. Some of the tumour cells showed numerous small vacuoles at the periphery; in others, these vacuoles were much larger and had led to destruction of the cell body. In certain areas few tumour cells could be seen, but numerous small cysts were present. It was possible to trace all the stages in this process, from vacuoles in the cells to complete destruction of cells and cyst formation. This appearance is rare in gangliocytomas of the brain, but in our experience it is common in similar tumours arising from the sympathetic nervous system. In our series, vacuoles were seen in the cells of certain growths (Cases 1, 2 and 9), but these had not progressed to degeneration and formation of cysts.

It must be emphasized that these cysts are quite different from the larger cysts which are probably the result of necrosis in areas of a tumour.

The tumour in Case 7 was different from all the others of this series, and closely resembles a growth described by Lhermitte and Duclos [7] arising from the cortex of the cerebellum. This was a diffuse tumour; it had produced marked thickening of the molecular layer of the cerebellar cortex, which was almost completely replaced by polygonal and pyramidal types of ganglion cells. In our case the tumour was in the cortex of the right parietal lobe, where the convolutions were flattened, and after excision were seen to be diffusely thickened. Histological study showed the cortex to be composed chiefly of pyramidal cells, but in addition oval and polygonal cells were present. The pyramidal cells did not have their apical dendrone directed toward the surface of the convolution, and the long axes of the other cells lay in every direction. Some very large pyramidal and polygonal cells were present; they contained well-formed Nissl granules, whereas the smaller cells contained finer granules, and the smallest were devoid of demonstrable chromatin substance except that seen in the typical nuclei and nucleoli. All these cells had an affinity for silver which outlined their bodies and dendrites. It was possible to see axis-cylinders arising from some cells, but implantation cones could not be found. Pigment such as is sometimes seen in normal cortical cells was present in only a few cells, which were probably inclusions or remnants of the normal cortex. Where the tumour merged into the normal cortex the Brodmann layers were irregularly involved, and in the tumour itself it was impossible to distinguish the various layers. The superficial layer (layer one or the molecular layer) in which, normally, cells are not present, contained large numbers of very small pyramidal and oval cells lying in contact with the pia mater. In some of the large pyramidal and polygonal cells neurofibrillæ were present, and occasionally these were clumped together as they are in cases of senile dementia.

In Case 8 the neoplasm was in the substance of the spinal cord; it has been described briefly elsewhere [6]. The cells of the growth were large and polygonal. They contained Nissl substance in granules finer than those found in the normal cells of the anterior horns of the spinal cord, and they did not contain any of the pigment which is so common in these cells. Dendrites were almost always present, although they were rudimentary Axis-cylinders could not be identified arising from any of the cells of the tumour; any axis-cylinders present were probably

inclusions of the invaded tissues of the spinal cord. The grouping of the cells, and their nuclei and nucleoli, were quite characteristic of gangliocytoma.

In Case 9, the tumour was similar to that removed in Case 8. This growth was almost completely encapsulated and enucleable, except at its upper and lower poles; this is not a usual experience at operation in cases of primary tumour of the spinal cord. The cells resembled those in the previous case, except that they showed a tendency to vary in shape; however, polygonal cells were dominant. Nissl granules were larger, especially at the periphery of the cells. The nuclei and the grouping of the cells were characteristic. With the silver impregnation method dendrites and cell bodies were well outlined, and axis cylinders arising from some cells were demonstrated; however, they were immature and stained relatively poorly. No well-formed axis-cylinders, such as might be included from invasion of the spinal cord, were present. This was probably the result of the encapsulation of the tumour; in the presence of such a growth the normal axis-cylinders would be pushed aside, and this is a possible explanation of the marked return of function after operation in this case. The stroma of the growth did not contain any adult or primitive glial cells, or glial fibrillæ. Lymphocytes and areas of necrosis were absent. In one area numerous neuroblasts of bipolar type were found, but the majority of the cells were almost completely differentiated ganglion cells. Therefore, the tumour was classified as a gangliocytoma.

The histological pictures presented by these nine tumours have several points of resemblance. In the majority marked uniformity of cell type was present, with the exception of the tumour in Case 4, in which several varieties of neuroblasts, as well as ganglion cells, were present. Throughout the entire group the nuclei of the neuroblasts, as well as those of the ganglion cells, were characteristic; they were large and vesicular, and each contained a deeply staining central nucleolus. All the tumour cells had an affinity for silver. It was unusual to observe axis-cylinders arising from any of the cells of a growth, and only in the more highly differentiated cells did neurofibrillæ traverse a cell. The majority of the ganglion cells were polygonal, although in one tumour pyramidal cells predominated; however, this was a tumour of the cerebral cortex. The neuroblasts varied greatly in size and shape, and few contained demonstrable Nissl granules; on the other hand practically all the better differentiated cells had definite Nissl substance.

There was a tendency for the adult ganglion cells to grow in groups,

but this arrangement was not so marked as that found in gangliocytomas arising from the sympathetic nervous system. In three tumours of this group (Cases 1, 2 and 9) some cells showed vacuolization of the cytoplasm, and in one tumour (Case 6) this had proceeded to destruction of the cell and formation of cysts; again, this is a more constant finding in gangliocytomas of the sympathetic nervous system. The amount of stroma varied; in several tumours stroma could not be demonstrated. The most interesting difference between any two tumours in this series occurred in Case 1; the original tumour was a neuroblastoma, made up of quite primitive cells, and after partial removal it recurred six years later as a well differentiated gangliocytoma with a stroma of heavy hyaline connective tissue.

There was nothing unusual in the situation of any of these nine tumours, except that in Case 6, which was attached to the dura mater, and not to the brain; grossly it simulated a parasagittal meningioma. There are three possible explanations for this unusual feature; first, that there was a small pedicle joining the brain, which was overlooked at operation, or second that there had been such a pedicle which had disappeared so that the tumour derived its blood supply solely from the meninges; neither of these two explanations is satisfactory. The third and most plausible explanation is that the neoplasm arose from a small heterotopic mass of cortical tissue lying free in the subarachnoid space anterior to the frontal lobes. Heterotopic masses of glial and other cerebral tissues are more common than is generally supposed; frequently we have observed them in the subarachnoid space. However, it has been our experience that such masses are more common around the base of the brain, especially in the posterior fossa, and around the spinal cord, than on the lateral or superior surfaces of the cerebrum. In a study of primary tumours of the spinal cord, Kernohan, Woltman, and Adson [6] encountered three gliomas which did not have any attachment to the cord itself; they felt that these tumours probably arose from heterotopic masses. So far as we can ascertain, this is the only gangliocytoma of the central nervous system which did not have its origin in the substance of the brain or spinal cord. Until further observations are made on other similar tumours, some doubt will remain regarding the real site of origin of this specimen.

This report was limited to a group of cases in which difficulty in the differential diagnosis of glioma, and neuroblastoma or gangliocytoma, did not arise. However, we have encountered several tumours in which both neuroblasts and spongioblasts have been growing side by side;

these have been omitted. Undoubtedly, some authorities will not agree that both types of tumour cells can and do grow together. It is now a recognized fact that medulloblasts are bipotential cells, and frequently we have observed neuroblasts and spongioblasts in medulloblastomas; Bailey and Cushing [1] have reported similar observations. In one case that we have studied, the patient had three separate neoplasms in the left cerebral hemisphere. That in the occipital pole was a spongioblastoma multiforme; that in the parietal lobe was also a spongioblastoma multiforme, but in addition contained many characteristic neuroblasts. In the tip of the left frontal lobe was a third small tumour about 1·5 cm. in diameter, and immediately behind this was a large, smooth-walled cyst about 5 cm. in diameter. The small tumour contained numerous well-formed polygonal ganglion cells growing in small groups, with characteristic cytoplasm, dendrites, nuclei and nucleoli; in addition to the ganglion cells many adult astrocytes of the fibrous type were present, with numerous neuroglial fibrillæ. This case has not been included in the present series because of the complications introduced by the presence of the other growths: it will be reported in a future paper.

Ecology.—The number of cases in the present series is too small to provide any but the broadest outline of the life history of growths of this nature. The cerebral growths may be considered first.

The interval between the onset of symptoms and the establishment of a diagnosis varied widely: thus in Case 1, in which the tumour occupied a temporal lobe, it was five weeks, whereas in Case 4, in which the tumour occupied the third ventricle, it was two years. These intervals are the opposite of those which might have been predicted, for tumours of a temporal lobe are often slow in declaring their presence, whereas tumours of the third ventricle as a rule rapidly give rise to symptoms of increase in intracranial pressure. In Case 4, however, the growth had not obstructed the flow of cerebrospinal fluid. It is somewhat paradoxical that of all the patients in our series the one with the shortest pre-operative history (Case 1) lived longest after surgical intervention. In Cases 2 and 3 the patients died soon after arrival; in neither case would operation have been of benefit. In Case 6 the extracerebral situation of the tumour lent itself to radical operation; this patient was alive two years after craniotomy, but it was at least possible that the growth had recurred. Study of the specimens obtained at operation or at necropsy showed very clearly that these growths are rarely sufficiently well demarcated from the surrounding cerebral tissue

to give the surgeon confidence to attempt their radical removal. Only in two instances (Case 1, 1925 tumour, and Case 6) was the tumour encapsulated, and in Case 6 this property may well have been an accident incidental to the extra-cerebral origin of the growth. It is significant that the tumour (Case 7) which was microscopically most highly differentiated, and for this reason most suitable for radical surgical attack, passed imperceptibly into normal brain. It must be concluded, however reluctantly, that tumours of this nature are rarely suitable for operations other than palliative.

The two growths which occurred in the spinal cord also differed one from the other in their enucleability. That found in Case 8 was not encapsulated. It is conceivable, however, that a diagnosis might have been reached a year or more earlier, when a more radical operation might have been possible. On the other hand the growth encountered in Case 9 was encapsulated throughout most of its extent, and therefore was largely removable; however, its upper and lower poles invaded the tissue of the cord, and consequently were irremovable. In this case it is possible that the period of survival and the amount of function retained may be partly accounted for by the persevering use of roentgenotherapy to retard the growth of the portions of tumour remaining in the cord.

Summary.

Nine cases are presented of tumours occupying the central nervous system which were derived from primitive nerve cells. The microscopical appearance of each tumour is described. Tumours of this nature are rarely suitable for radical operation.

PLATE LEGENDS.

Fig. 1 (*Case* 1).—Cellular neuroblastoma removed in 1925. The cell bodies are not clearly outlined, but the round vesicular nuclei and deeply staining central nucleoli are well shown. The cells do not possess definite dendrites. Toluidine blue. × 500.

Fig. 2 (*Case* 1).—Gangliocytoma removed in 1931. The outlines of the nuclei are indistinct, but the nucleoli are sharply stained. Nissl substance can be seen collected at the periphery of the cells. In the cytoplasm of one cell a vacuole is present. Toluidine blue. × 1100.

Fig. 3 (*Case* 2).—The cells tend to grow in small groups, in an œdematous stroma. Variation in the shape of the cells is evident, and the characteristic nuclei and nucleoli are well shown; binucleated and multinucleated cells are present. Toluidine blue. × 500.

Fig. 4 (*Case* 3).—The cells of the tumour contain characteristic nuclei and nucleoli; one cell is multinucleated. Fine Nissl granules are scattered diffusely throughout the cytoplasm of the cells. Toluidine blue. × 1100.

FIG. 5 (*Case* 4).—Part of a coronal section through the brain, to show the tumour occupying the lower half of the third ventricle; many cysts are apparent in its substance. Its line of demarcation is moderately distinct; the thalami are scarcely invaded by the growth, which has displaced them laterally. Weigert's stain for myelin sheaths. × 1·5.

FIG. 6 (*Case* 5).—Anterior views of coronal sections through the brain, to show the tumour occupying the inferior part of the anterior horn of the left lateral ventricle. It has occluded the left foramen of Monro, and invaded the septum pellucidum and the head of the left caudate nucleus. In the photograph on the right the small tumour on the lateral wall of the right lateral ventricle is visible. Reduced.

FIG. 7 (*Case* 5).—Gangliocytoma in the third ventricle. The cells have indistinct outlines, and multinucleated types are present. The nuclei and nucleoli are characteristic. The cells possess dendrites; in these, and in the cytoplasm, Nissl granules are present. Toluidine blue. × 475.

FIG. 8 (*Case* 5).—Astroblastoma on the lateral wall of the right lateral ventricle. The cells have abundant homogeneous cytoplasm and delicate processes. The nuclei contain many chromatin granules; a few cells contain two nuclei. Hæmatoxylin and eosin. × 500.

FIG. 9 (*Case* 6).—The cells contain characteristic nuclei and nucleoli, and in some fine Nissl granules are present. Stroma is absent. Toluidine blue. × 500.

FIG. 10 (*Case* 6).—An area of tumour selected to show the formation of cysts. These begin as small vacuoles in the cells. Toluidine blue. × 375.

FIG. 11 (*Case* 7).—There is considerable variation in the shape of the cells, but pyramidal forms predominate. Binucleated cells are present. Axis cylinders are arising from some cells, and in some cells neurofibrillæ are present. Orlandi's silver-impregnation method. × 375.

FIG. 12 (*Case* 7).—An area of the tumour selected to show the excess of ganglion cells in layer one of the cortex (the marginal glial zone), as well as in layers two and three. The irregularity in the size of the cells and in the direction of their axones is marked. Orlandi's silver-impregnation method. × 325.

FIG. 13 (*Case* 7).—An area of the tumour selected to show the cells growing in groups in layers five and six of the cortex. Each island gives a false impression of being one multinucleated cell. Satellitosis is present around certain included cortical cells. Toluidine blue. × 500.

FIG. 14 (*Case* 9).—The cells tend to grow in small groups; they have characteristic nuclei and nucleoli. The stroma is œdematous. Toluidine blue. × 500.

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PLATE VIII.

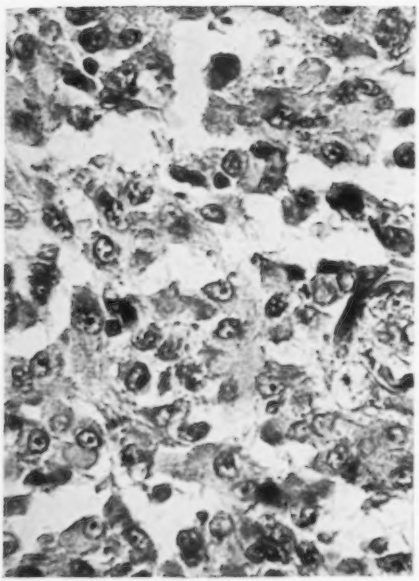

FIG. 1.

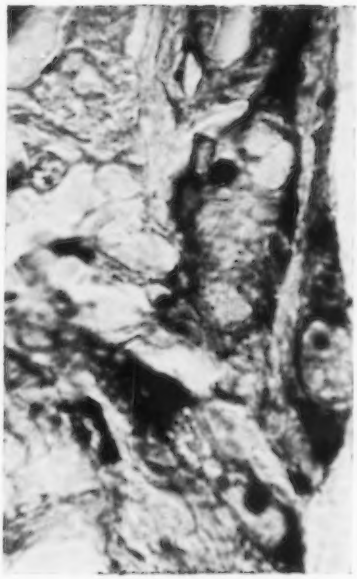

FIG. 2.

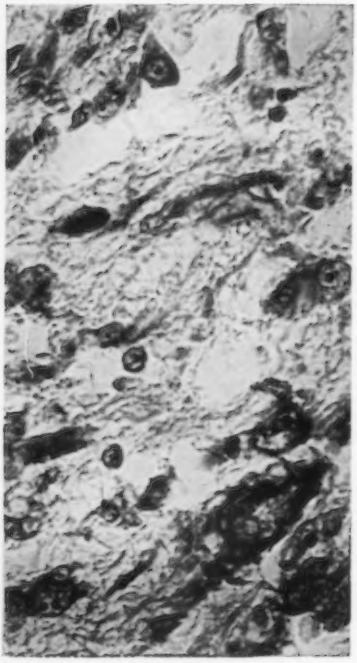

FIG. 3.

FIG. 4.

To illustrate paper by Kernohan, Learmonth and Doyle.

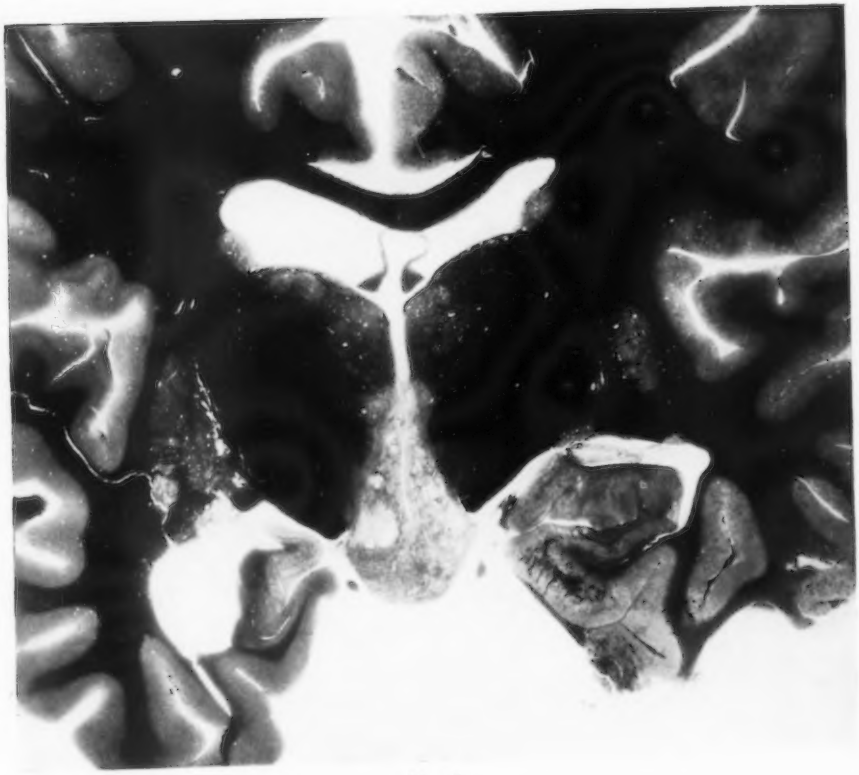

FIG. 5.

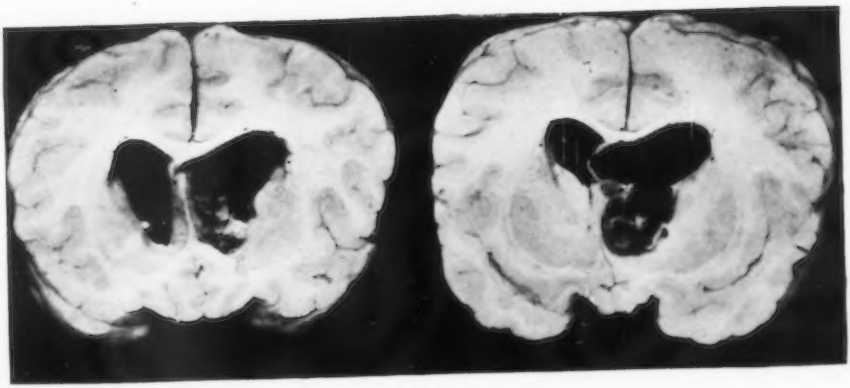

FIG. 6.

To illustrate paper by Kernohan, Learmonth and Doyle.

PLATE X.

FIG. 7.

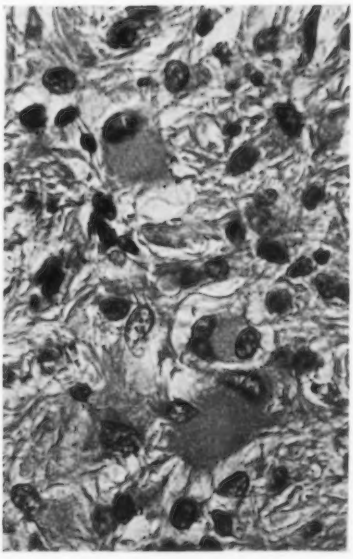

FIG. 8.

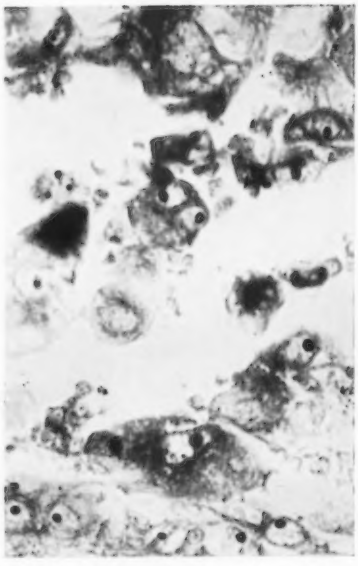

FIG. 9.

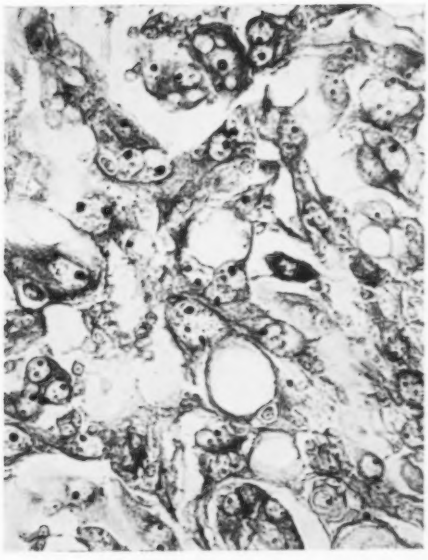

FIG. 10.

To illustrate paper by Kernohan, Learmonth and Doyle.

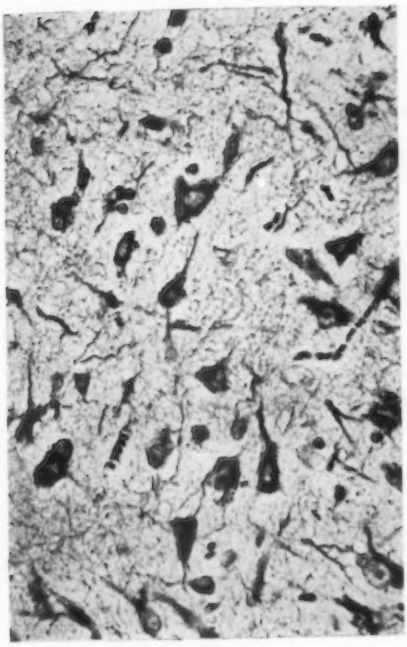

FIG. 11.

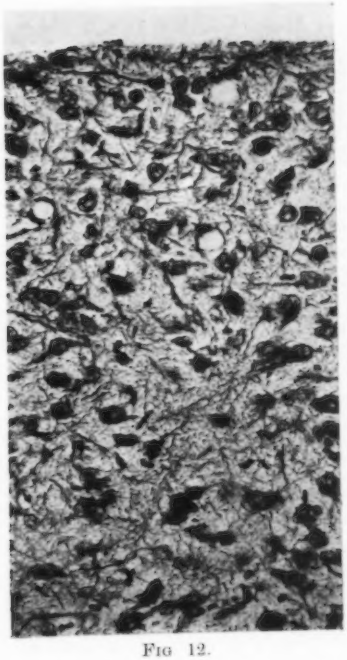

FIG 12.

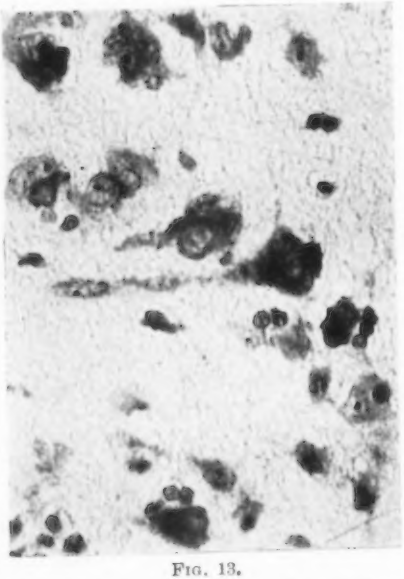

FIG. 13.

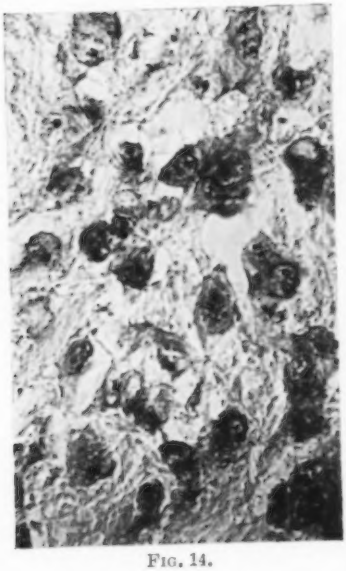

FIG. 14.

To illustrate paper by Kernohan, Learmonth and Doyle.

TUBEROSE SCLEROSIS AND ALLIED CONDITIONS.

BY MACDONALD CRITCHLEY AND C. J. C. EARL.

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CHAPTER I.—HISTORICAL SURVEY.

THE first recognitions of that special form of cerebral sclerosis which we speak of as "tuberose" or "tuberous" are based upon a few isolated pathological descriptions. Probably the earliest record was a case described by von Recklinghausen [56] in 1863. In the brain of a newly-born child a large number of sclerotic areas were found; there were several myomata growing from the heart muscle. We have been unable to secure the original communication, and further details are not available. Hartdegen [34], early in 1881, described a child of two days, of healthy parentage, who died in convulsions. Autopsy revealed spina bifida, purulent spinal meningitis, areas of sclerosis throughout the cerebral cortex and a number of small tumours projecting into the lateral ventricles. The cerebral lesions were made up of glial hyperplasia, containing a number of ganglion-like cells of exceptional size, the processes of which, together with those of the glia cells, formed a close network. Hartdegen applied the term "glioma gangliocellulare cerebri congenitum" to this case.

We are indebted to the Medical Research Council for the defrayment of the expenses of this paper.

Bourneville [13] was perhaps the first to recognize the condition as a pathological entity. In a series of publications between 1880 and 1898 [13-22], he drew attention to a rare form of multiple cerebral sclerosis occurring in young patients who had shown during life mental deficiency and epilepsy. This condition he called "tuberose sclerosis" from the potato-like appearance of the morbid foci. His accounts were mainly pathological and he did not consider it possible to diagnose tuberose sclerosis during life. He was inclined to attribute the disorder to the results of a meningitis or a meningo-encephalitis.

Bourneville noted a frequent co-existence of tumours of the kidney of a primitive "mixed" histological character.

More detailed histological studies of the brain were made in the following years, notably by Geitlin, Brückner, Pellizzi [52], Perusini [53], de Montet [48], Campbell [26], and Vogt [63]. In recent years, outstanding pathological contributions have been made by Bielschowsky and his associates [6, 7, 8, 9, 10], Josephy [41], and von Meduna [67].

Subsequent reports confirmed the association of neoplasms of the kidney with tuberose sclerosis, and growths were also at times found in the heart, spleen, lungs and retina.

Bourneville noted the co-existence of another anomaly, namely, adenoma sebaceum. This had been described by Balzer (1885-86) [2, 3] and also by Pringle [55], as a hyperplasia of certain elements in the skin, distributed in a curious butterfly fashion upon the face, and associated not infrequently with epilepsy and intellectual subnormality.

Bourneville regarded the occurrence of adenoma sebaceum as coincidental, and for years tuberose sclerosis was looked upon as a pathological curiosity. Later, however, principally owing to the work of Vogt in 1908, the clinical syndrome of mental deficiency, epilepsy and adenoma sebaceum emerged, and series of such cases were reported by Sherlock (9 cases) [61], Lind [46], and Brushfield and Wyatt (16 cases) [23]. It also became evident that incomplete forms of the syndrome occurred. Schuster, in 1913 [59, 60], described a case of tuberose sclerosis with adenoma sebaceum occurring in a young man of normal intellect though subject to epilepsy. It was recognized, too, that the cerebral condition might exist in the absence of one or even of all of the classical clinical signs. Recent contributions have dealt largely with its pathogenesis, histology, the clinical aspects of abortive and atypical forms, and with the association of the disorder with von Recklinghausen's disease.

One of the chief difficulties in the description of such a protean disorder involving numerous systems of the body and exhibiting various *formes frustes* is the question of terminology. The term epiloia, originally proposed by Sherlock, is applied by psychiatrists to connote the complete syndrome of mental deficiency, epilepsy and adenoma sebaceum. The name has been severely criticized, but it serves a purpose and is now sanctioned by use. For the less complete forms in which any one of the pathological findings may exist alone no suitable name appears. Tuberose sclerosis is perhaps the most constant feature, and we feel that in the absence of an adequate inclusive title we should adopt tuberose sclerosis as the most informative, restricting epiloia to the severest grades, and designating the abortive monosymptomatic forms by some purely descriptive label, e.g., "renal tumour," "adenoma sebaceum."

Chapter II.—The Clinical Aspect.

Our present series comprises twenty-nine cases, all of which, with the exception of No. 23, were personally studied. Twenty-two were patients at Caterham Mental Hospital; five of them were inmates of the Fountain Mental Hospital, one was a patient of the Manor and one died at Leavesden Mental Hospital. To Drs. Lindsay, J. Nicoll, E. Littlejohn and R. M. Stewart, the respective medical superintendents of these four institutions, we accord our thanks for their kindness in allowing us to examine and record these cases. Four patients in our series died and the central nervous system and the visceral growths were studied in detail.

Etiology.—Tuberose sclerosis appears to be commonest in European countries, especially Great Britain, although cases have also been recorded from Australia and the United States, and once from Brazil. Almost all the subjects were of white race, Jews and Gentiles alike being affected, and, as with other types of cerebral degeneration, tuberose sclerosis is commoner among the "lower classes" of the community.

The family history frequently presents important facts, as evidence of tuberose sclerosis or various abortive forms of the syndrome amongst the siblings or progenitors, though it is probable that the true nature of the *formes frustes* is frequently not appreciated. The point is well illustrated in Berg's account [4] of a father and daughter who showed adenoma sebaceum, epilepsy and slight mental impairment, with typical post-mortem findings of tuberose sclerosis and renal tumours. The grandfather had died after a renal operation and at autopsy a

"mixed" tumour of the kidney was found without other features suggestive of tuberose sclerosis.

Schuster's first case, a boy aged 16, showed during life adenoma sebaceum, epilepsy and signs of intracranial tumour. Autopsy revealed tuberose sclerosis and multiple renal tumours. The boy's mother had numerous *café au lait* patches and a black nævus on the left arm; his maternal grandmother had multiple nævi, his mother's grandmother was an epileptic, and convulsions in childhood had occurred in his mother's sister. A paternal cousin of the mother was also epileptic.

In Koenen's family six individuals were affected in three generations. A family recorded by Dobson [28] is an example of grossly degenerate stock on both sides. A girl, aged 10, died at Wakefield Asylum of epiloia. Her brother was epileptic and very unstable; the mother was "nervous," and two maternal uncles had died in convulsions in early childhood. A maternal grand-uncle was alcoholic and died of general paresis; a maternal grand-aunt had "alcoholic pseudo-paresis." A paternal uncle was intemperate.

Often the family history shows no evidence of tuberose sclerosis but bears a strong psychopathic taint. Epilepsy and alcoholism are common and in many cases psychoses have occurred. In de Montet's case manic-depressive psychosis occurred in the ancestry, and a family history of dementia paranoides was obtained in the second of the cases reported by Kreyenberg, Delbanco and Haack [43]. A parent died of tabo-paresis in Lázár's case [44].

In our series a family history was obtainable in twenty instances only, marks of psychopathy being present in the following thirteen cases:—

Case 1.—Both parents alcoholic.

Case 5.—Grandfather died at 26 with epilepsy.

Case 6.—Uncle insane.

Case 7.—Father at present in an asylum suffering from epilepsy, paranoia, and adenoma sebaceum of the face. A brother is an epiloiac.

Case 8.—Maternal cousin in an asylum.

Case 10.—Father alcoholic. Mother and aunt feeble-minded. One sister "dull." Two siblings died in infancy.

Case 11.—Maternal grandfather epileptic.

Case 14.—Mother, mother's cousin and mother's uncle have facial adenoma sebaceum.

Case 16.—Mother's sister in asylum.

Case 17.—Mother had facial adenoma sebaceum, but no gross mental defect. An uncle and one brother died insane. Father emotional and unstable.

Case 20.—Maternal cousin epileptic.

Case 21.—Mother in an asylum. Patient's elder brother has adenoma sebaceum. Mother's brother "rash on face," and "simple-minded."

Case 24.—Father died in an asylum. Brother died in an asylum with epilepsy.

It has not been possible to investigate the family history of all our cases more fully to determine how many of the psychotic members actually showed evidences of tuberose sclerosis.

Factors of possible importance are the questions of place in family, the age of the parents at the time of conception, the state of the maternal health during pregnancy and the details of the confinement. In fourteen cases only in our series was it possible to obtain details as to place in family; the facts are as follows:—

Case 1.—Third of seven children.
Case 2.—Fourth of five children.
Case 5.—Second of four children.
Case 8.—Third of four children.
Case 11.—First of two children.
Case 12.—Third of five children.
Case 13.—Third of six children.
Case 19.—Third of three children.
Case 21.—Third of three children.
Case 24.—Third of five children.

These findings contrast with those in Brushfield and Wyatt's series, where eight out of sixteen patients were first-born.

The age of the parents at time of conception has unfortunately been noted only fourteen times in our patients. The average of these gives 33·14 and 30·71 years as the age at time of conception of the father and mother respectively. In ten of Brushfield and Wyatt's cases the age of both parents was over 30 at the time of birth.

Details as to the mother's confinement and labour have not been available in many of our cases nor in cases on record. In one of our series, the notes state that the patient was a six months' premature child (though it weighed $7\frac{3}{4}$ lb.) and that labour was preceded by a fright.

All writers on this subject now agree in exculpating syphilis as a factor in the ætiology of tuberose sclerosis, although Scarpatetti [68] regarded parental syphilis as the responsible agency.

Symptomatology.—The clinical features are difficult to describe under one head.

In the incomplete forms, which are common amongst the members of the family of an epiloiac, there may be no resultant disability, so that the real nature of the *forme fruste* is usually undiscovered.

In the true epiloiac symptoms and signs appear in infancy or early childhood. It is usually stated that the earlier the onset the more rapid the course. The first case on record is actually also the youngest, for Hartdegen's patient died at the age of 2 days.

Usually the first abnormality is developmental delay such as characterizes mentally defective children in general, the child failing to sit up, crawl or walk until an unusually late age. Talking is usually very late and many lower-grade patients remain mute. Out of thirteen of our patients in whom there was a note on speech development, two commenced to talk at 12 and 13 months respectively, one at 4 years, one at 7, one at 9, whilst 8 failed to develop speech.

The degree of mental defect varies widely from case to case. It is usually obvious by the third year, and in all our cases in which the point can be ascertained mental defect was observed before the sixth year.

Cutaneous lesions make their appearance usually within the first decade, and may advance somewhat abruptly at puberty. The skin affection which attracts attention consists in a red papular rash over the nose and cheeks, recognizable as adenoma sebaceum. It is impossible to say at what age the other dermatological lesions appear on the trunk and extremities, and it is a matter of experience that these may be overlooked by the parents, until attention is directed to them in the course of medical examination.

At about the time of the second dentition the patient may begin to lose ground and show increasing dullness, disordered conduct, spitefulness, emotional outbursts and impairment of speech. In many such instances admission to an institution became necessary. The course of the epiloia is rapidly downhill after puberty; death usually takes place in the second decade from cachexia, pulmonary disease or status epilepticus. One of our patients, however (Case 14), dropped dead quite suddenly while at play. In this case gross cardiac disease was found at autopsy. In Lind's series the oldest patient died at 47, the youngest at 4; in our four fatal cases, death occurred at 14 in one instance, and at 17 in the other three.

In the incomplete variants of this disorder, the clinical course may differ considerably. Thus, in those cases where adenoma sebaceum is in the foreground, neuro-psychiatric features may be inconspicuous and not progressive. No shortening occurs in the expectation of life

and the patient may remain a useful working member of the community.

A still rarer development and mode of termination is exemplified by those cases which show in early adult life signs of raised intracranial tension, at times accompanied by focal neurological signs (Schuster, Kaufmann and Fischer, Bychowski [25]). We have been privileged to examine the brain of a case of this type. A girl, aged 8, was admitted to the Richmond Hospital, Dublin, under the care of Mr. McConnell, on account of headache, vomiting and defective vision. Petit mal attacks had been present for many years, but there was no gross mental defect. Examination revealed bilateral papillœdema but no localizing neurological signs. At post-mortem examination there were found cerebral changes typical of tuberose sclerosis, and in addition a gliomatous tumour the size of a walnut in the posterior portion of the third ventricle.

Lastly, a few patients have succumbed after operations for the removal of a visceral growth the symptoms of which form an important part of the clinical picture.

Epilepsy, which constitutes a frequent and important symptom in both typical and atypical cases, varies widely in its clinical features. In the epiloia group it is especially frequent, being absent only twice from our series of twenty-nine cases, and once also from the Brushfield-Wyatt cases and the series recorded by Bourneville. It usually makes its appearance within the first two years of life.

All types of attack may be encountered, grand mal, petit mal and Jacksonian. Equivalents are not uncommonly present, in the way of giddy attacks, paroxysmal outbursts of passion, "absences" and the like. Two of our patients exhibited varieties of epilepsia procursiva.

The frequency and periodicity of attacks are very variable in individual cases. While some patients have as many as ten or twelve fits daily, others, such as our Case 10, have merely one or two in a year. Attacks of serial epilepsy may occur, though the intervals of freedom may be extremely irregular. One striking feature in many epiloiacs—which distinguishes them from other cases of epilepsy with mental defect—is the very long periods of remission which may be present. Some of our patients, who were previously suffering numerous attacks, would suddenly go for a period of years without a fit. In Case 24—where the patient showed no mental impairment—there was a remission of seven years. These periods of freedom occur irrespective of treatment. During these remissions the mental deterioration usually continues steadily,

thus emphasizing the lack of correspondence between the severity of the epilepsy and of the idiocy. Gallus has stated that the epiloiac never develops the characteristic "epileptic temperament" which might be expected in an individual sustaining a large number of attacks.

As a terminal feature, the epileptic fits may increase considerably in number; thus during the last twenty-four hours of life, our Case 5 had 111, and Case 19, 119 fits.

Neurological manifestations.—The physical appearances of the patient with tuberose sclerosis are usually striking enough to betray the diagnosis immediately. The presence of the facial eruption at once arrests attention and closer examination usually reveals other abnormalities.

Most of the individuals are noticeably undersized for their years, without however showing any infantilism or absence of secondary sexual features. Stigmata of degeneration are usually demonstrable in the lower-grade patients. In our experience the commonest marks have comprised: (1) the simian hand (flattening of the thenar eminence, with inversion of the thumb and flexion of the terminal phalanx); (2) shortness and incurving of the little finger; (3) ears which are misshapen, asymmetrical, protruding or excessively large. Numerous other stigmata have been encountered, such as hemihypertrophy, epicanthus, high palate, supernumerary digits, hydrocephalus, syndactyly, spina bifida, and cranial anomalies. Lázár mentions adiposo-genital dystrophy in a patient with tuberose sclerosis. Several patients in our series were highly myopic; a few showed strabismus. It is interesting that enamel defects, irregular arrangement of the teeth, and other dental abnormalities are absent.

Neurological examination is at times entirely negative; more often, however, minor anomalies are demonstrable in the motor system. The low grade of the mental state and the not infrequent resistivity usually precludes satisfactory investigation.

The ocular mechanisms are usually healthy, as instanced by normal pupillary reactions and ocular movements, absence of nystagmus and normal media. Van der Hoeve [36 and 37] has drawn attention to the occurrence of flat tumours or "phakomata" on the retinæ of patients suffering from tuberose sclerosis. Although he judged this finding not uncommon, having seen it in both eyes of every one of his six patients, we have found them once only in our series. More recently, they have also been noticed in cases of tuberose sclerosis by Feriz and by Nitsch. These "phakomata" appear on ophthalmoscopic examination as oval or circular areas, white or grey in colour, situated in the retina away from

the disc. Their diameter is about half that of the papilla. No close relationship with the blood-vessels exists; there is no surrounding tissue reaction.

Papillœdema does not occur in tuberose sclerosis, except in those very rare cases of coincident intracranial neoplasm.

More detailed examination of the motor system shows usually no focal muscular atrophy; the crude strength—as far as accurate testing is possible—appears normal in the patients who have no local paralysis. An alteration in muscle tonus is common, however. In the younger individuals definite diminution in tone is usual, allowing of undue mobility at the joints; in older patients this hypotonus is usually replaced by rigidity. As a rule it is impossible to investigate this point more closely, as a certain amount of negativism is generally present. Catatonia is often found, especially in this latter type of patient.

Highly characteristic of the mentally defective patients with tuberose sclerosis is a peculiar type of motor restlessness which is described later.

Accurate investigation of sensibility is not possible. In such patients as are able to co-operate at all, the special senses and cutaneous sensation appear to be normal. Some of the lower-grade patients are indifferent to any but grossly painful stimuli.

Local paralyses are at times met with in this condition, comprising a monoplegia, hemiplegia, paraplegia, or tetraplegia. A hemiplegia was found once in our series and a diplegia twice. In these two latter cases the diplegia was of the "atonic" variety, with absent tendon reflexes, flaccidity and plano-varus deformity of the feet.

Cerebellar signs occurred once only in our series, and we know of no record of similar finding in the literature.

Case 25.—A female, aged 35, was of such defective mentality as to be unable to furnish any history whatever. No records were available as to the development of her symptoms. She was an epileptic and showed numerous cutaneous anomalies, such as diffuse pigmentation of head and back; a large *café au lait* patch over left axilla and scapular region and another under the left breast; vitiligo over neck; scanty, pale type of facial adenoma sebaceum. She had a constant nodding movement of the head, and the speech was grossly dysarthric and staccato. Nystagmus occurred on lateral deviation of the eyes; hypotonus and a cerebellar type of inco-ordination were demonstrable, associated with an intention tremor. The tendon reflexes were extremely brisk; plantar responses flexor in type. No obvious sensory loss. Optic discs normal. Gait wildly reeling

Owing to the lack of family and personal history, it is impossible to say whether these signs indicate a chance co-existence of tuberose

sclerosis with an heredo-ataxia, or whether there is a more intimate association.

Speech is usually grossly impaired in well-marked cases.

The reflexes are generally unaltered in the earlier stages, but in older patients with hypertonus there may be some liveliness of the tendon responses. Plantar responses are of the flexor variety, except in the diplegic cases. We have found no abnormality in the abdominal responses.

Psychological.—Tuberose sclerosis is an heredo-familial degeneration, and those afflicted may be expected to show some degree of mental inferiority. The psychological aspect of subjects suffering with the various *formes frustes* has never been studied, but, as our cases show, a strong familial psychopathic taint is common, whilst the great majority of patients with adenoma sebaceum are known to be mentally defective though not necessarily epiloiac.

In our series one patient was mentally normal. Three others were defectives without epilepsy; all three were adult females, their mental ages on the Terman Binet scale being 8 years, 5 years 2 months, and 5 years 4 months. Emotionally the first of these was entirely stable, the second facile and excitable, and the third wildly unstable and subject to fleeting persecutory delusions.

The essential feature of the psychology of epiloia is a combination of intellectual defect proper with a primitive form of psychosis. The intellectual defect is always pronounced, all of our cases falling into the categories of imbecility and idiocy. The psychosis always resembles a primitive type of catatonic schizophrenia, though the exact form of the reaction varies with the level of mental development at which it occurs.

The depth of psychosis is independent of the degree of intellectual defect, although the two processess are so inextricably intertwined as to render impossible any accurate estimation of the part played by either in any given case. In the following account, therefore, the grouping for descriptive purposes into "high" and "low" grades is somewhat arbitrary and is based largely upon the adaptive reactions, with relatively little reference to the potential intelligence.

The high-grade patients are usually relatively intelligent in childhood. Signs of defect appear early and there is delay in walking and talking, but the children are quite trainable in an imbecile school and may even learn to read and write a little. Screaming fits are very common—they occurred in all the cases of which we have obtained reliable records—and the children usually play with their fingers a good deal. Otherwise

they appear temperamentally normal and are sometimes described as cheerful and affectionate. The earliest signs of psychosis occur as a variability—independent alike of fits or of discoverable external cause—in the degree of environmental adaptation achieved. This is first seen at or after the fifth year, occurring as periods of hours or days during which the patient appears vague and preoccupied and is mentally inaccessible. At or before puberty some degree of dissociation is usually permanently installed, though subject to wide and prolonged variations in degree. At this time, too, rapid deterioration may occur, so that patients who have hitherto ranked as high grade must now be relegated to the low-grade group.

Those who remain sufficiently high-grade now show marked personality changes, the states of preoccupation are longer and more frequent and the patients grow solitary, silent and apathetic and liable to sudden brief outbursts of motiveless excitement similar to those seen in catatonic schizophrenics. They usually resent interference and become dangerous to other patients and sometimes to themselves, though the self-injury is always slight and suicidal attempts do not occur. Speech which may have been fairly fluent now falls off, they use very few words and may show echolalia and short perseverative repetition of phrases, or may become almost entirely mute. Three of our cases showed the "secret speech" of dementia præcox.

The degree of catatonia varies. A certain amount of rigidity may be present and flexibilitas cerea is common. Several of the patients appear semi-stuporose and one girl has lain in a negativistic stupor for months on end.

The tendency to hand-and-finger-play remains, though it is not so marked as in the low-grade group. The more psychotic patients are usually to be seen sitting apathetic, their hands clasped on their laps with fingers slowly twisting. Two of the least psychotic of the high-grade patients, who commit self-injury when annoyed, do so by violently biting their hands.

The mental content of the psychosis cannot be assessed, as these people have not sufficient intelligence to communicate their thoughts, but it is significant that in three of five patients from whom drawings could be obtained, these showed grossly psychotic trends with idio-significant details and crude sexual symbolism. The fourth drawing was of bizarre type and the fifth, which was obtained from the least dissociated of our patients, was the usual imbecile production but showed marked perseveration, the entire page being covered with drawings

and letters in response to the command, " Draw a man " ! This patient gave a psychotic response in the " manikin " test. The following case illustrates this particular type of epiloia :—

Case 14.—E. B., female, aged 28. *Family history* : Maternal grandmother and grand-uncle had adenoma sebaceum. On admission at age of 24, showed adenoma sebaceum. She was simple, childish but quarrelsome ; speech slow and hesitant. Epileptic fits occurred at monthly intervals. On examination, she lay in a catatonic attitude, smiling to herself. The speech was hushed and barely audible. Simian hands. A gross catatonic tendency existed in arms and legs. Tonus was diminished in the arms and increased in the legs. Tendon-jerks brisk ; pupillary responses rather sluggish. Adenoma sebaceum ; large sacral plaque of molluscum fibrosum ; a few fibromata over the trunk.

The low-grade group shows a similar, though more primitive reaction. Mental development is later and less complete than in the high-grade cases and deterioration commences earlier. Speech development is absent or very poor, and in the developed psychotic stage mutism is constant. Such children are not silent, however, for they make curious animal-like sounds, and by varying intensities can often make known their wants or feelings. The variation in accessibility is not so striking as in the higher-grade patients, though probably always present. Screaming fits and causeless crying are very frequent. Violence and self-injury are less common than in the high-grade group.

All manner of bizarre attitudes and stereotyped movements occur, and these are most striking in the hands and fingers. Somewhat similar hand movements sometimes occur in simple aments of the idiot grade, but they are uncommon and are very rarely complex, whilst in the low-grade epiloiac they are a constant feature, frequently indulged in, and often of an amazingly complicated nature. These movements appear to have some significance for the patients ; they occur when the appearance of dissociation is most marked, and the eyes usually fixate the moving hand. Thus one boy has been seen with a rapt expression keeping up a highly complicated rapid movement of his right hand and slow and entirely different movement of the left, completely indifferent to his neighbour who was hitting him vigorously on the head with his open hand. Another boy who has frequent fits of crying holds his hand in a curious attitude in front of his eyes when he is crying. Primitive erotic movements of rocking and swaying are always present and usually frequently indulged in. Less common features observed in this group are head banging of a very violent type, rumination and aerophagy.

Dissociation is frequently profound, the patient appears completely

unconscious of his surroundings and tolerates an extraordinary amount of physical interference. Such patients take no interest in their food except to play with it, and are liable to lose much weight from under-nourishment. Catatonic rigidity is constant and flexibilitas cerea frequent, though the relative activity of most of these patients renders the term stupor hardly applicable. Patients in this group cannot be credited with "thought" and it is impossible even to guess at their subjective processes, but from the sudden fixation of their gaze upon nothing and from their air of listening—again to nothing—intently and with a strange and alien smile, it seems possible that they undergo some crude hallucinatory experiences.

This low-grade type of patient is illustrated by the following case report:—

Case 2.—E. A. F. T., male, aged 11. Family history unimportant. Patient is said to have been born three months prematurely though the weight at birth is reported as 7¾ lb. He walked and talked at one year; convulsions first appeared at 15 months and have continued at intervals. On admission at the age of 4 years and 3 months, he was a low-grade imbecile, wet and dirty, requiring to be fed. He could not understand sentences but would repeat words. Within the next few years, adenoma sebaceum was noticed on the face. His mental state deteriorated and he showed a fondness for regurgitation and rumination. On examination he was found curled up; he was unable to talk but chattered rapidly and quietly to himself. He resisted examination. No neurological abnormality existed other than slight hypotonus. When excited he showed bizarre hyperkinetic movements of the hands and fingers. No stigmata of degeneration. Marked adenoma sebaceum; a round, flat fibroma on the neck, with several smaller nodules on trunk; one area of pigment over the right scapula and numerous small apigmented patches (see fig. 2).

In the most profound cases there is complete apathy and occasionally even a failure to chew or to swallow. In this group it is impossible to say how much of the final result is to be ascribed to dissociation, and how much to amentia, though it is almost certain that both factors are always present. Any variation in accessibility is most difficult to demonstrate, though there is usually a history of some deterioration and there may be occasional "flashes" of spitefulness. One exceptional case, a helpless idiot, showed an improvement in her 13th year, and now at 16 is classed as a low-grade imbecile able to walk and talk.

It was possible to submit five epiloiacs to psychometric tests. These patients are particularly difficult test subjects on account of their verbal paucity or mutism, and their marked inaccessibility. The test-series adopted was the Merrill Palmer scale for pre-school children, all

verbal tests and all tests involving direct imitation being scored as omissions, thus using the tests as a performance series.

FIG. 1.

FIG. 2.

FIG. 1.—Showing a number of pedunculated dermal tags on the neck in the case of an epiloiac patient.

FIG. 2.—Well-marked facial adenoma sebaceum in a patient with epiloia.

TABLE I.—PSYCHOMETRIC TEST RESULTS (MERRILL PALMER SCALE).

Case No.	Sex	Age	Mental age	Intelligence quotient	Degree of dissociation
4	M.	19	2 years 3 months	16·0	Severe; almost inaccessible
5	M.	17	5 ,, 10 ,,	41·6	Slight
6	M.	19	5 ,, 11 ,,	42·25	Semi-stuporose
13	F.	16	3 ,, 8 ,,	26·14	Slight
14	F.	28	5 ,, 3 ,,	31·5	Semi-stuporose

The results, which are shown in Table I, are presented because of the striking evidence they afford of the potential intelligence of the subjects as compared with their adaptive behaviour. The proper

evaluation of the scores obtained is doubtful, involving, as it does, the application to adolescent and adult defectives of a scoring intended for normal young children. Moreover, the quantitative results of psychometric tests on psychotic subjects must always be accepted with reserve; there is no doubt that in this series the scores obtained were definitely below the subjects' true potentiality.

Qualitatively the tests gave valuable information. The subjects appeared to understand the instructions given to them, and such tests as were accepted were intelligently approached, muscular co-ordination and the handling of concrete material being surprisingly good.

Behaviour under test showed obvious indications of psychosis in all cases. Two patients failed in block building tests because they became dissociated and built designs of their own instead of following instructions, whilst all the patients showed a tendency to dissociation on meeting with difficulties. In one case this caused the only failure, the rest of the performance being well above the imbecile level. One patient lost a great many marks because he insisted on holding all his fingers extended throughout the test, which rendered his performance very slow.

The varying degrees of dissociation were well displayed. Four of the five patients tested were apathetic, and two of these were practically stuporose. These last were most striking, being roused with great difficulty from semi-stupor, performing a test cleanly and showing quite a degree of interest, only to relapse into their former state immediately afterwards. One boy who had kept up an amazing series of attitudinizations and elaborate movements of his hands, suddenly ceased, and filled the Wallin peg boards quickly and neatly, in thirteen and fourteen seconds respectively, to return at once to his movements, whence no further stimulation could arouse him.

Dermatological.—We now realize the great importance and diagnostic significance of cutaneous anomalies in the symptomatology of tuberose sclerosis.

The chief of these skin lesions is, of course, facial adenoma sebaceum. To-day we rely strongly on this physical sign in making the diagnosis, and one would hesitate to diagnose tuberose sclerosis in the absence of adenoma sebaceum, except among those members of a family of tuberose sclerosis who show neurological or psychical abnormalities.

According to Sutton, adenoma sebaceum was first described by Rayer, but priority is usually given to Balzer. Five years after Balzer's first communication Pringle described carefully the clinical and histo-

logical characters of the disease, and suggested the term "adenoma sebaceum." From that time a large number of cases have been recorded by dermatologists, and certain aetiological and clinical peculiarities have been noted. Thus it was found to occur early in childhood or occasionally at birth, usually increasing rapidly at puberty. Only exceptionally did the onset date from early adult life. The heredo-familial tendency and the frequent association of intellectual defect and of epilepsy were noted.

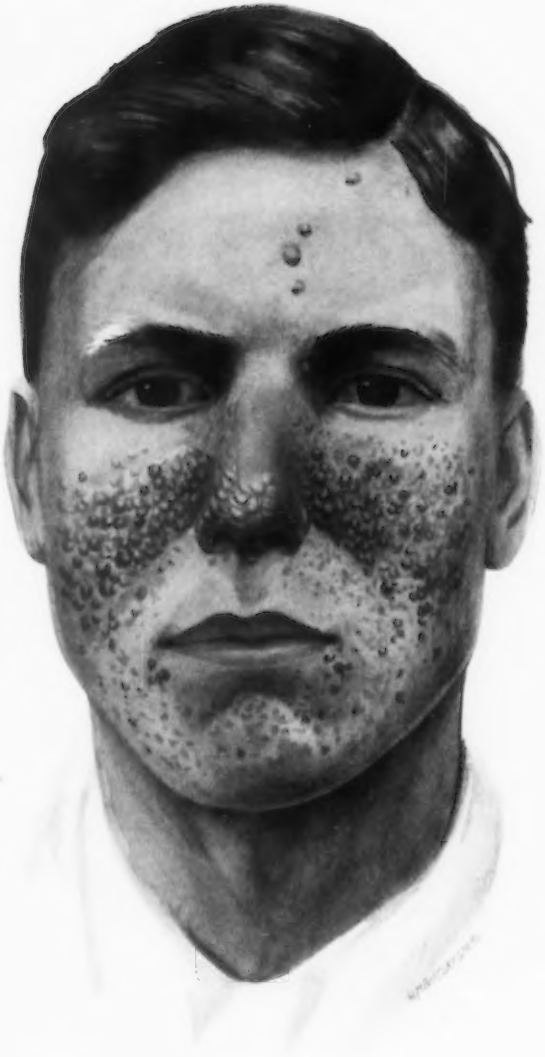
The clinical features of adenoma sebaceum comprise a nodular rash of red, yellowish-red or brownish colour distributed over a special region of the body. Thus it appears extensively over the face, showing itself first, according to Brushfield and Wyatt, in the naso-labial folds, later spreading so as to cover entirely the nose and the middle of the cheek over the infra-orbital region, in a butterfly-shaped area. The rash later spreads laterally but rarely shows itself inside the frontier of the naso-labial fold except to appear on the chin. Occasionally a few nodules are seen in the temples, or on the brow. In contrast to the florid redness of the nose and malar region, there is often a striking circumoral pallor.

The rash consists of numerous papules measuring on an average 4 mm. in diameter. They are somewhat hard in consistency and project above the skin for 2 to 5 mm. They are reddish in colour and at times translucent or jelly-like. They fade on pressure to a great extent, but may not do so entirely. Thus, in the centre a minute telangiectatic point or even a fine network of injected capillaries may be present. In certain areas, as for example over the tip and dorsum of the nose, the papules become confluent and form a smooth plateau of red shiny appearance, interspersed at times with telangiectases.

In Pringle's case the telangiectatic elements were rather striking, so that to-day many authors distinguish a "Pringle's type" of adenoma sebaceum from a "Balzer type," according to the degree of capillary injection. A third variety, spoken of as the "Hallopeau-Laredde" type, is sometimes described, consisting of vascular nodules of particular hardness from excessive fibrous tissue development.

It has often been noted that the facial lesions deepen in colour at the time of an epileptic attack and more especially during a succession of fits in cases of the serial type of epilepsy. Subjective symptoms are rare, though Pringle mentions that the rash may be painful in cold weather. Frequently the same area of skin is affected by an acne rosacea which waxes and wanes according to the state of the digestion and the proximity of a meal.

PLATE A.



Facial adenoma sebaceum in a case of epiloia.

To illustrate paper by Macdonald Critchley and C. J. C. Earl.

Microscopical examination, as shown by Pringle and others, reveals: (1) A thinning of the dermis; and (2) an extensive overgrowth of the sebaceous glands (see fig. 3). This histological structure leads some writers to imagine a neoplastic development of sebaceous glandular structure, a conception which is implied in the term "adenoma sebaceum," possibly allied to the so-called epithelioma sebaceum cysticum, but nowadays dermatologists usually regard adenoma sebaceum as a simple hypertrophy of the sebaceous glandular structure of the skin. According to Jadassohn, Poir and others, it more correctly belongs to the category of "sebaceous nævus."

FIG. 3.—Histological appearance of a patch of adenoma sebaceum, taken from Case 24. (Courtesy of Dr. Franklin.)

Adenoma sebaceum, though a very common accompaniment of tuberose sclerosis, is not invariably present. The earlier writers did not mention it specifically, and it is possible that its presence was ignored. Bonfigli, however, in describing his cases, stated definitely that no cutaneous affection was present. In our series, adenoma sebaceum was entirely absent from one case (No. 23) and was extremely slight in another (No. 10). It may be unrecognized by neurologists who perhaps attribute the facial appearance to the results of bromide medication.

A variety of adenoma sebaceum consists of a few discrete nodules, each no larger than a shot, scattered over the butterfly-area of the face

These differ from the typical papules in being pale and completely avascular; they never coalesce and there is no surrounding tissue-reaction. Indeed, the nodules may well escape cursory examination especially in artificial illumination; they are promptly recognized by their intense hardness when the pulp of the finger is lightly passed over the cheek. This particular variety is probably identical in the so-called "Balzer type"; it is rarer than the "Pringle type," occurring in four only of our series.

Fibromata.—Of the other cutaneous abnormalities, the commonest are small, flattened fibromata scattered over the trunk, particularly on the back. In at least ten out of our twenty-nine patients, fibromata were present. Usually they are multiple though numbering as a rule not more than a dozen. They vary in diameter up to 2 cm. They grow usually in the superficial layers of the skin, though once in our series a subcutaneous fibroma was found. In another of our patients several scalp fibromata occurred, each the size of a marble. Subungual fibromata have been recorded in this disease by Hintz [35] and by Busch [24].

A variant type of fibroma is one in which large numbers of miliary fibrous tubercles are scattered over the trunk. These are slightly raised papules, smaller than a pin's head; indistinguishable in colour from the surrounding skin; in size and appearance they resemble coarse "goose-flesh." This miliary type occurred in two of our patients and also in one recorded by Schuster. In Buschke's case, each seed-like milium was pierced by a lanugo-hair.

Another highly characteristic skin lesion is the so-called shagreen patch. This occurs as an uneven thickening of an area of skin, raising it a little above the surrounding surface. Each plaque is irregularly shaped and of about a palm's breadth. They are usually single and are commonest over the lumbo-sacral region. Their colour is that of the surrounding skin and may be discoverable only by close inspection or by palpation. Shagreen patches were found in four of our twenty-nine cases.

Pigmentary disorders are often present and take two main forms: first, a diffuse bronzing of wide regions of the skin; and, secondly, oval or circular areas of brown pigment, known as *café au lait* patches. These latter are indistinguishable from those met with in von Recklinghausen's disease.

At times a vitiligo-like arrangement is found, an area of pigmentation being abruptly succeeded by an area of abnormal whiteness. Such appearances are commonest upon the trunk, and there may exist an approximate segmental distribution recalling a thoracic dermatome (cf. Case 3).

Not infrequently patches occur which are of abnormal whiteness. They resemble in size and conformation the *café au lait* stains, but differ in absence of pigment instead of an excess. Lesions of this nature were found in two cases. Pigment may disappear from the hair in places, and in one of our patients a patch of local canities occurred on the outer half of one eyebrow.

In some patients there occurs over the neck or shoulders a cluster of small pedunculated dermal tags, varying in number from one to a score. This appearance of this molluscum fibrosum pendulum was encountered in two patients; in Case 9 they were particularly conspicuous (see fig. 1) and there is a striking resemblance to an illustration in Berg's paper of 1914.

Naevi are commonly described in cases of tuberose sclerosis, but were seen in two patients only in our series. Fox has reported a purpuric rash on the limbs and trunk.

Other simple and mixed types of cutaneous tumour have been recorded exceptionally in tuberose sclerosis; thus there are on record instances of lipoma (Dore [69]); fibromyolipoma (Kischer); angiofibrolipoma (Bielschowsky).

Another rare cutaneous anomaly which has been recorded by Kreyenberg and his colleagues is a generalized hypertrichosis.

Chapter III.—Morbid Anatomy.

Central Nervous System.—The naked-eye appearance of the cerebrum presents characteristic features. It is not usual to find any obvious abnormality either in the cranium or in the meninges, although at times both these structures have been somewhat thickened. Ossification of the sutures has been noted at times. The pia-arachnoid usually strips easily. The cerebrum itself may be somewhat less than the normal in size and weight, though this smallness is never excessive. No marked disturbance occurs in the arrangement and disposition of the gyri, although it has been noted at times that the secondary and tertiary divisions of the sulci may be incomplete.

Characteristic of the disease is the presence in the convolutions of numbers of whitish, slightly prominent areas. These may occur in any part of the cerebral hemisphere, and there is no apparent area of predilection. In number they vary from one or two to twenty or thirty. They range in size from $\frac{1}{2}$ cm. broad and long, up to nodules measuring 2 cm. or 3 cm. in each dimension. The smaller areas are limited

to the conformation of a convolution, and are usually present upon the summit of a gyrus. The larger ones extend over two or three adjacent convolutions and may affect the depths of the sulci as well as the summits of the gyri. These areas are distinguishable from the surrounding cortex by a slightly paler tint; the contrast is not great, however, and the sclerotic regions are recognizable much less by inspection than by touch. On palpation of the hemispheres the affected regions are at once betrayed by their firm consistency, giving rise to a hardness which has been likened to cartilage, rubber or potato (hence

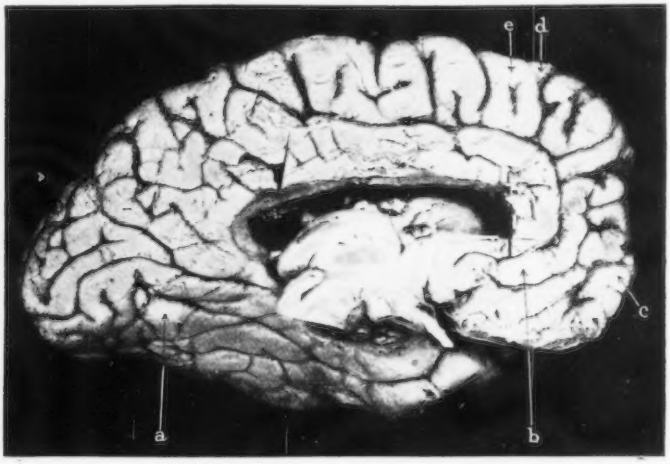


FIG. 4.—Mesial aspect of the left hemisphere from a case of tuberose sclerosis. Areas of sclerosis are marked a, b, c, d, e. Note also the "candle-gutterings" in the lateral ventricle.

"tuberose"). Palpation frequently reveals smaller and darker nodules which escape even careful scrutiny.

At times some of the larger sclerotic areas are umbilicated, but this is, on the whole, exceptional. Pellizzi has distinguished two types of sclerotic nodules according to their macroscopic appearance. In the one, elongated tubera lie along the course of a gyrus, while in the other more sharply demarcated, circular areas stretch from one convolution to another. The surface in the first type is usually smooth, convex, or slightly flattened, while in the second variety the surface may be somewhat roughened and also umbilicated.

Cross-section through the hemispheres displays more clearly the distribution and appearances of the foci (fig. 5). The relative pallor

of the affected grey matter is striking. At times the sclerotic nodules degenerate in their centre so as to form small cysts; more commonly minute calcareous fragments are encountered within the foci.

The cerebral hemispheres are usually the sole region of the central nervous system affected. In exceptional instances tubera have been described in the cerebellum (Brückner; Vogt, Case 3), the medulla (Geitlin), the spinal cord (Perusini) and the retina (van der Hoeve; Feriz).

In the walls of the third and lateral ventricles, immediately beneath the ependyma, small irregular projections are found, arising usually

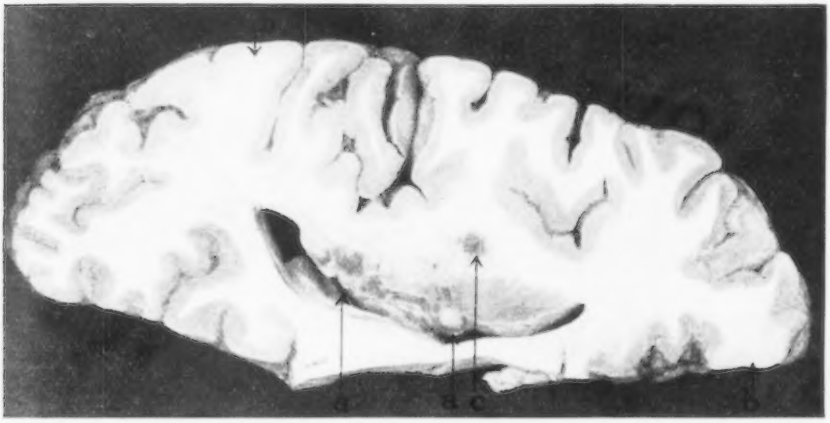


FIG. 5.—Cross-section of a hemisphere; a, "candle gutterings" in the wall of the lateral ventricle; b, cortical tuberose patches; c, patch of sclerosis in the white matter.

from the thalamus. These appear as tiny, button-like tumours, or, in larger examples, as "candle-gutterings" (Lind) running from above downwards and following (Campbell) the tributaries of the vein of the corpus striatum (figs. 5 and 6).

Microscopical appearance.—The histological structure of these sclerotic zones in the cortical and subependymal grey matter comprises broadly a marked anarchy in the stratification of the nerve-cells with regressive changes in the neurones themselves; considerable overgrowth of glia cells and their processes, and the appearance of curious large cells of a type foreign to the mature nervous system. Each of these processes warrants detailed study and description. Although the tubera appear to the naked eye as sharply-demarcated regions, it becomes obvious from microscopical examination that no abrupt transition exists

between healthy and diseased areas. On the contrary, it is found that one zone merges gradually into the other.

In addition to the macroscopic foci themselves, the intervening and apparently healthy regions demand attention. Histological investigation of the cortical zones around and between the foci shows changes of a profound character differing merely in degree from those in the tubera. Furthermore, alterations of a microscopic character may usually be

FIG. 6.—Section of the wall of a lateral ventricle to show the appearance of "candle gutterings" in cross section.

revealed within other regions of the central nervous system, and particularly in the cerebellum and in the spinal cord. The morbid process active in cases of tuberose sclerosis is, therefore, much more diffuse than the naked-eye examination would suggest.

Nerve-cell changes within the foci.—Portions of cortex stained by Nissl, Bielschowsky and hæmatoxylin-van Gieson methods, show a relative pallor in the sclerotic zones. Under the microscope the individual cell laminæ cannot be demonstrated. Pyramidal cells may be present in the more superficial layers, and granular elements may be

seen scattered among the larger neurones of the deeper parts. The orientation of the pyramidal cells may be altered so that the bases are no longer directed downwards and the apices upwards.

The total number of cellular components is somewhat reduced, and the morphological state of many of the cells is changed. Thus, one may observe alterations in the outline, with clumping and later disappearance of the Nissl granules and a lateral position of the nucleus. Thickening of the processes may occur, and the cell as a whole become shrunken. Fatty degeneration is present, though not in profound degree.

Silver-staining methods may show the intracellular fibrillary network heavily impregnated with silver deposits so as to recall strikingly the Alzheimer cell changes seen in senile dementia. This resemblance is enhanced by the occasional appearance of argentophil depositions arranged in an annular fashion, not unlike the appearance of a very early senile plaque.

Glial alterations—A marked proliferation of the neuroglia constitutes one of the outstanding features, and is betrayed by the density of the affected zones in sections stained by the Victoria blue or Mallory method. There is a considerable overgrowth of glia fibrils which are mainly of the thin type. At times, however, the fibres may be of such thickness as to belie their glial character, and Campbell mistakenly described them as fibrous in type. The proliferation is most marked in the cortex, though it extends for some distance into the underlying white matter. Peculiar interlacing arrangements of the fibres are described and likened to "crossed-swords," or "ruffled-hair"; arrangements of this type are conspicuous in the more superficial zones of a sclerotic focus. No increased density of the glia is seen around the blood-vessels.

In the subependymal growths the neuroglial fibrillary proliferation produces a loosely interlacing complex of parallel strands. The ependymal covering remains intact, and between this layer and the glial overgrowth is an interval occupied by loose areolar tissue; in this zone a venule may run, according to Campbell, but in none of our sections was this feature apparent.

A less obvious increase in the number of neuroglial cells is seen, and large astrocytes are frequent. No conspicuous overgrowth of microglia takes place, though Bolsi [12] described a perivascular proliferation of the Hortega cells. Qualitative changes in the glia occur and they frequently respond to staining methods such as that of Bielschowsky, to which ordinarily they do not react.

At times glial proliferation takes on such a localized and excessive type of overgrowth as to show itself on naked-eye inspection as a definite tumour-like mass. Such a condition appears exclusively in the intraventricular growths, and small tumours may develop up to the size of a walnut and may be accompanied during life by symptoms of raised intracranial pressure. The histological structure is always that of glial tissue, but individual cases vary according to the proportion of cellular or fibrillary elements. Thus, in the original case of Hartdegen the term "glioma gangliocellulare" was applied; Brushfield and Wyatt refer to the large nodule in their fatal case as a "glioma," and specify that it was composed chiefly of slender spindle-shaped cells with long

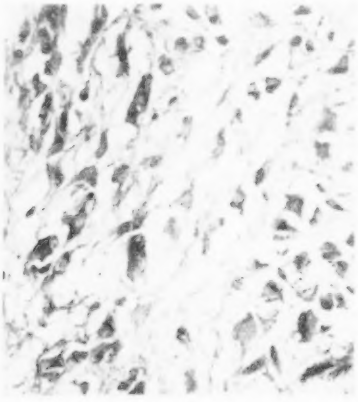


FIG. 7.—Microscopical appearance of a gliomatous tumour in a case of tuberose sclerosis.

interlacing processes, forming bands and whorls of fairly open tissue and containing in their meshes numerous thin-walled capillaries and free red blood-corpuscles. In Schuster's case two conspicuous intraventricular tumours were encountered; the larger one, the size of a plum, consisted in a gliomatous mass of large cells, fibres being entirely absent. Many of the constituent cells possessed a homogeneous protoplasm and many nuclei. A case recorded by Bielschowsky and Berliner revealed, in addition to numerous foci of tuberose sclerosis, an intraventricular neoplasm the size of a "plumpit." The histological picture was that of a tumour formed of proliferating blastomatous cells; no concretions were found as in the case of the other "candle-gutterings." The authors believe that the neoplasm was of more recent date, and they speculate as to whether or not this new growth began to develop

on the basis of a previously existing old nodule. According to Globus [33], the glial paraventricular tumours belong to the group of spongioblastoma multiforme. In McConnell's case of gliomatous tumour associated with tuberose sclerosis, the histological picture is that of a large-celled astrocytoma (see fig. 7).

Giant cells.—Perhaps the most striking and the most important feature is the presence of abnormal cells of large size in relation with the sclerotic foci. Since Hartdegen's original description, they have been noted by all writers on the pathology of tuberose sclerosis, and have occasioned much discussion as to their nature and their bearing upon our conception of tuberose sclerosis in general.

These cells lie typically in the depths of the sclerotic nodules, i.e., where the neuronic and glial changes are most intense. Both cortical and subependymal tubera may contain such cells, though they are more numerous in the former situation. It is important to realize, however, that they may occur outside of the cerebral cortex; thus they appear as heterotopies in the white matter near the tubera. Furthermore, they may be demonstrable in the cortex away from the sclerotic regions, and they have also been noted in more remote portions of the nervous system such as the cerebellum, medulla and spinal cord.

Much controversy has arisen as to the nature of these large cells, and in particular as to whether they are derivatives of glial or nerve elements. It appears definite, however, from careful histological study that all the large cells of a particular case do not possess the same morphological and staining characters and probably represent entirely different cells, their sole common feature being their large size. A study of the personally observed specimens bears out what seems to be the tendency of modern histological opinion, namely, that the large cells are of varying appearances, but tend to approximate either to the nerve-cell or to the glia-cell type. All manner of transition forms link up these extremes.

In this way we may distinguish: (1) a large cell of neuronic type; and (2) a large cell with glial resemblance.

(1) *Large cells approximating to the neuronic-cell type.*—These usually preponderate slightly, and are more numerous in the cortical than in the subependymal growths. They are well demonstrated by the ordinary nerve-cell stains and particularly by Bielschowsky's method; they do not react to glial stains. In size, they vary from a large pyramidal cell up to that of a Betz ganglion cell; and when secondary changes occur, further distension may increase their bulk still more.

As a rule they occur in clusters of three or more, and may be surrounded by some densification of the glia. They are occasionally triangular or polyhedral in outline, but the larger specimens are elliptical or even circular.

The internal structure of these cells shows various abnormalities in the position and staining reactions of the nuclei. Considerable variability exists in the character of the processes; sometimes they are short and thick, and at times a stem arises which quickly breaks up into finer branches. Globus has illustrated a giant cell of this type with a very long and tape-like process, extending through several microscopic fields.

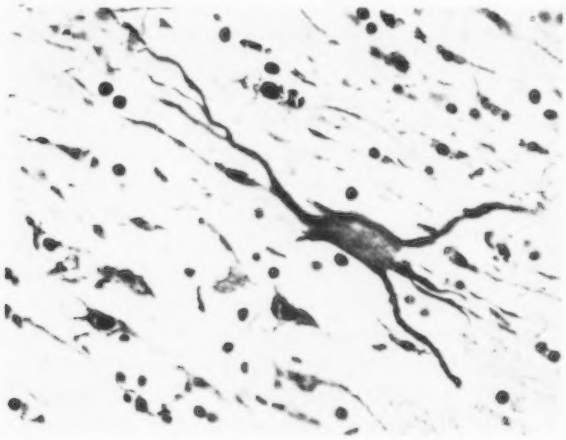


FIG. 8.

The neuronic character of this type of giant cell is suggested by the presence of intracellular fibrillary network and also of Nissl (tigroid) granules.

(2) *Large cells of glia type.*—Cells of this order are somewhat less numerous than the others and occur more particularly in the ventricular nodules. They are also grouped in the vicinity of blood-vessels, to the walls of which they may be attached. Their shape is unlike that of a nerve-cell, being oval or circular. There are no intracellular fibrillæ or granules, and the processes are invisible except in silver-stained preparations. With such methods the processes are displayed, sometimes recalling those of a nerve-cell, but at other times numerous short and curly processes radiate at intervals from the periphery.

Other changes which may be present within the sclerotic regions include alterations in the blood-vessels; several writers have drawn attention to a dilatation of the vessels which may attain sinusoid proportions. Hyaline degeneration within the vessel walls, affecting especially the adventitia, has also been described. In many instances, however, changes in the blood-vessels are slight or absent.

Deposits of calcium salts or of hyaline material are often seen lying amid the whorls of glial fibrils, especially in the ventricular nodules.

Although the lesions of tuberose sclerosis are most marked in the

FIG. 9.

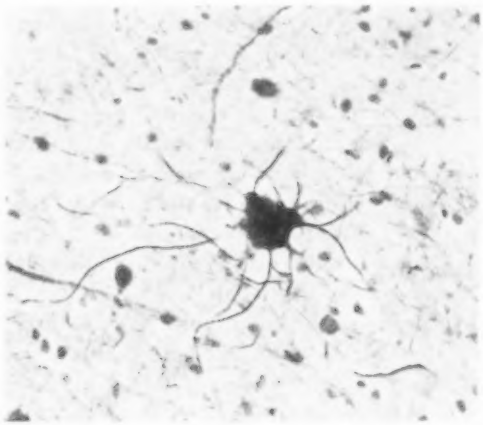


FIG. 10.

cortical or subependymal grey matter, they may occasionally occur in the central grey masses of the brain. Thus, in two cases of Bielschowsky and Freund [9], changes similar to those in the cortex were spread over the basal ganglia, affecting the caudatum chiefly and the putamen to a lesser extent. The globus pallidus was only slightly implicated.

Changes in the cerebellum have been described, but are uncommon. In our cases no abnormality was present. Pollak [54] found atypical giant cells in the cerebellum; abnormal ganglion cells were also seen by de Montet. Orzechowski and Nowicki [50], and Brushfield and Wyatt, mentioned a slight reduction in the number of Purkinje cells. The glia cells may be increased in number. Von Meduna [67] described in his case a reduplication of the granular layer in the cerebellar cortex.

Nodular lesions within the cerebellum appear to be still rarer. Bielschowsky found macroscopic lesions here in one case only out of twelve. In this case there were localized lesions typical of tuberose sclerosis lying in the white matter of the cerebellar hemispheres, and demarcated in an unusually sharp manner from the surrounding tissue. Otherwise the cerebellar cortex showed little in addition to a parenchymatous atrophy with glial replacement, and the appearance recalled that seen in juvenile paresis or the heredo-ataxias. Only an occasional large cell betrayed the diagnosis.

The heart.—The cardiac anomaly classically associated with tuberose sclerosis is rhabdomyoma. The condition is a rare one, only forty-two cases having been reported. In thirty-two cases there was a note as to the condition of the brain, and in no fewer than twenty-five of these cases tuberose sclerosis was present (Furber). Ten cases had kidney tumours, tuberose sclerosis, and cardiac rhabdomyomata.

The tumours are usually small and multiple, appearing as greyish rounded masses, sometimes embedded in the muscle itself and sometimes projecting into the cavity of the heart. The commonest sites are the septum, trabeculæ, papillary muscles and anterior wall, and the tumours lie usually immediately beneath the endocardium. Microscopically they consist of irregularly arranged striated cells of primitive type varying from 50 to 200 μ in diameter (Wolbach [65]) and having nuclei varying in number from one to four. The tissue is honeycombed with wide vacuolated spaces containing glycogen (Rehder [57], Mönckeberg [47]).

Steinbiss [62] finds that these tumours undergo fibrosis and never show malignant changes. Their exact nature is a little obscure. They are evidently of prenatal origin, and metaplastic rather than neoplastic in nature.

The cardiac findings in Case 15 of our series are worth recording. The boy was known to have an enlarged heart, and a diagnosis of aortic stenosis with incompetence had been made. Autopsy showed the heart weighed 23 ozs. Subaortic stenosis of congenital type was present, a dense membrane running round the aortic vestibule immediately below the base of the valve and narrowing the orifice to $\frac{1}{2}$ cm. In addition, the whole of the papillary muscle and trabeculæ of the left ventricle were shrunken and fibrosed, the process extending for 3 mm. into the heart wall. Microscopy showed fibrous tissue only, and sections from various other portions of the wall revealed no abnormality. The endocardium and pericardium were both normal.

Kidneys.—Renal tumours are found in about 80 per cent. of cases of tuberose sclerosis. They are rarely diagnosed in life, though in Hyman's case nephrectomy was necessary—a large necrotic hypernephroma being removed. In our series no renal signs have been observed during life.

The tumours are usually multiple and bilateral and vary in size from a pin-head to a large orange. They are nearly always cortical, and though not encapsulated they are sharply demarcated. They rarely, if ever, form metastases.

Histologically they are of embryonal mixed type, the precise appearance varying from case to case. Thus angiosarcoma, liposarcoma, myosarcoma, myolipoma, fibrolipoma, perithelioma, and hypernephroma have all been described.

Of those four cases in our series which have come to post mortem multiple kidney tumours were found in each. In Cases 15 and 17 they were classified as peritheliomata, whilst in Case 5 the tumours were of primitive mixed sarcomatous type, and one the size of a walnut had become necrotic.

Duodenum.—Duodenal tumours have been described in one case (Sailer [58]). At autopsy upon an epiloiac idiot, aged 15, a number of small nodules were found in the wall of the duodenum; microscopically these growths were necrotic and structureless in their central part with small round cells at the periphery. They were considered to be sarcomatous in nature. Adeno-sarcomata were found in both kidneys.

Chapter IV.—Clinical Variants.

With fuller knowledge of the varied aspects under which tuberose sclerosis presents itself, the problem arises as to the status of the numerous atypical and incomplete forms.

Examination of the relatives of epiloiac subjects suggests that we are justified in regarding the following as probably representing incomplete forms of tuberose sclerosis :—

(1) Adenoma sebaceum alone.

(2) Adenoma sebaceum with epilepsy but no mental change.

(3) Adenoma sebaceum with symptoms of cerebral tumour.

(4) Visceral tumour alone (including retinal tumours).

Our present conception of this aspect of tuberose sclerosis is necessarily very elastic, and until we have more pathological data most of our ideas will remain conjectural.

(1) The first important variant concerns the finding of adenoma sebaceum alone. Dermatologists are familiar with this condition occurring in individuals of normal intelligence who have never suffered from epilepsy and who show no neurological abnormality whatever. It is arguable, of course, that such patients only rarely come before the neurologist and that slight nervous or mental changes might be present though not obvious on cursory examination. Such an opinion, though probably correct in many instances, does not apply to cases, for example, where close co-operation has existed between neurological and dermatological departments.

The question arises whether histological changes occur in the brain of individuals who during life have shown adenoma sebaceum alone. It is not unlikely, from our knowledge of tuberose sclerosis, that slight alterations might be found in the cortex of such individuals, differing only in degree from those occurring in epiloia. As far as we have been able to trace, no record is available of the cerebral findings in a case of isolated adenoma sebaceum.

The possibility of latent cerebral changes existing in patients with simple adenoma sebaceum is further borne out by the occasional development of insanity in middle-life in cases which up to then were of dermatological interest only.

(2) The following case report illustrates the co-existence of epilepsy with facial adenoma sebaceum in an individual of normal intelligence.

Case 24.—A. C., female, first attended the out-patient department of the National Hospital, Queen Square (Dr. C. P. Symonds) on account of epileptic fits, in February, 1927, being then 29 years of age. Her parents had died in her infancy, the father having been insane. She was the third of five children: her eldest brother suffered from fits and died in an asylum at the age of 30. The others are healthy, one sister is married and has a healthy child. No family history of adenoma sebaceum was obtainable. When the patient was 8 years old, adenoma sebaceum appeared on the face, and she had her first fit. From the ages of 14 to 21 no attacks occurred, but they recurred and persisted at irregular intervals. She attended the National Hospital for six months and then left to get married. She had one premature child which was born dead. She was referred again to one of us (M. C.) in the out-patient department of the National Hospital by the kindness of Dr. John Franklin who had been attending her for eczema of the nipples. She was at this time aged 33. On examination no neurological abnormality was found. She appeared of normal intelligence and is at present earning her living as an upper domestic. Facial adenoma sebaceum was present, of a comparatively avascular type: a portion of the affected skin was excised by Dr. Franklin for histological examination (see fig. 3). Apart from eczema of the nipples,

there were no other cutaneous lesions. No stigmata of degeneration except syndactyly of the second and third toes of both feet.

Here, a psychopathic family history strengthens the view of a relationship with tuberose sclerosis. It is probable that histological changes exist in the cerebrum, slight in degree but qualitatively identical with those in the complete forms of tuberose sclerosis.

(3) Schuster's first case exemplifies another clinical variant. An epileptic patient, of normal intellect, suffering also from adenoma sebaceum, developed in early adult life signs of intracranial hypertension. The autopsy revealed, in addition to the ordinary findings of tuberose sclerosis, the presence of an intracerebral glioma. Similar case reports have been made by Kaufmann and Fischer, and by Bychowski.

(4) The presence of primitive visceral tumours alone, without accompanying mental or nervous abnormalities and without adenoma sebaceum, may under certain circumstances constitute a *forme fruste* of tuberose sclerosis. Reference has already been made to Berg's case, where a child and her father both died with renal tumours and cerebral tuberose sclerosis; the grandfather died after operation for renal tumour. During life he had shown no evidence of neurological disorder, and there had been no adenoma sebaceum. We do not know, however, whether any histological changes were present in the cerebrum. Other cases are on record in which an individual, otherwise normal, has been under the care of an urological surgeon for a renal tumour, and where at post-mortem examination typical cerebral changes were discovered.

A certain number of pathological reports are on record of multiple rhabdomyomata of the heart associated with cerebral sclerosis. Unfortunately we do not know sufficient of the clinical picture to determine whether the cases were examples of complete tuberose sclerosis.

It is certain that the retinal tumours may occur without accompanying cutaneous mental or physical changes. Thus, van der Hoeve found a retinal tumour in the fundus of a patient aged 21, who showed no other abnormalities. The nature of the tumour was revealed when investigation of the family history discovered five brothers and sisters suffering from advanced tuberose sclerosis.

Chapter V.—The Nature of Tuberose Sclerosis; Relationship with von Recklinghausen's Disease.

The nature of tuberose sclerosis is still in doubt, but there is an increasing evidence to suggest a developmental anomaly commencing early in fœtal life. Older views were soon set aside; thus Scarpatetti's theory of tuberose sclerosis as a manifestation of inherited syphilis, and Fürstner and Stühlinger's conception of a fœtal leptomeningitis, were never sustained.

Most of the recent disharmony concerns the view taken of the nature of the pathological changes and particularly of the giant cells. Bielschowsky has tended to regard them as reactive compensatory formations consequent upon a primary glial hyperplasia. Most histologists, however, regard the giant cells as of duplex character and suggest that they represent a primitive type of cell not far removed from an undifferentiated neuroblast; they may develop characteristics which are either glial or neuronic.

Thus two views emerge as to pathogenesis. On the one hand tuberose sclerosis may be regarded as essentially a hyperplastic disorder of the neuroglia, originating during embryonic life and associated with hyperplasias in other extraneural structures. Thus Bielschowsky regarded the condition as comprising a "blastomatous growth-tendency of the spongiocyte." On the other hand, the view is held of a widespread metaplasia, affecting mainly the ectodermal tissues, but also to some extent mesodermal and endodermal derivatives, having its beginnings in utero. According to Feriz [30] tuberose sclerosis is a disorder of differentiation between parenchymatous and supporting tissues, leading to exaggerated and localized overgrowths.

An association between tuberose sclerosis and von Recklinghausen's disease has been emphasized within the past twenty years. Points of contact between the two disorders are seen firstly in the similarity of certain clinical features. Both disorders are characterized by striking cutaneous anomalies, and more particularly by pigmentary disorders, *café au lait* patches, fibromata, nævi. Both are heredo-familial affections often associated with psychopathic trends. Epilepsy is associated with both, though rare in von Recklinghausen's disease. In both conditions retinal tumours of identical appearance may be demonstrable.

The other suggestive line of argument concerns those rare but important cases in which marks of tuberose sclerosis have co-existed with those of a neurofibromatosis.

A curious and important case recorded by Orzechowski and Nowicki was that of a male patient of 18, in whom there were found at autopsy changes typical of tuberose sclerosis; in addition there occurred a centrally-placed neuro-epithelioma of the cord and medulla; a neuroma in the choroid plexus of the third ventricle; two tumours arising in the blood-vessel walls in the cortex; proliferative changes in the cells of the sheath of Schwann in the spinal roots and in the peripheral and cranial nerves; a similar growth in the muscular coat of the stomach: and a fibro-endothelioma of the dura mater. The authors regarded their case as indicating the identity of neurofibromatosis and tuberose sclerosis, the final picture depending merely upon the particular location of the morbid process. Orzechowski and Nowicki suggested that tuberose sclerosis should be renamed "neurinomatosis centralis," that peripheral neurofibromatosis should be spoken of as "neurinomatosis peripherica," and that the term "neurinomatosis universalis" should apply to cases like their own, in which the two disorders are associated.

A few other cases of this association are on record. Thus, Perdrau [64] is said to have demonstrated neurofibromatous growths in the kidney in a case of tuberose sclerosis. In Gamper's case [32] a patient dying with generalized von Recklinghausen's disease showed at autopsy numerous interesting anomalies within the central nervous system. These included two "neurinomatous" growths lying under the ependyma; multiple ventricular tumours of glial origin; sclerosis and blastomatous cell proliferation with demyelinization in the frontal lobes and in the vermis; circumscribed nodules in the cerebellar hemispheres. In a case of tuberose sclerosis mentioned by Globus a "neurofibroma conforming to the central type" was attached to the bundle of Vicq D'Azyr.

Various authors have pointed out the identity of certain of the cerebral appearances in tuberose sclerosis and in von Recklinghausen's disease. Thus, in both conditions there may be seen hyalin thickenings in the vessel walls (Feriz); abnormal monster cells (Bielschowsky); similar histological changes in the cerebellum (Maas, Orzechowski and Nowicki).

Van der Hoeve, who called attention to the presence of retinal tumours in tuberose sclerosis, pointed out that identical masses (or phakomata) may occur in cases of von Recklinghausen's disease. He, too, suggests a change in terminology, and would designate tuberose sclerosis as "phakomatosis Bourneville," and neurofibromatosis as "phakomatosis Recklinghausen."

It must be pointed out that the occurrence of cases of these mixed types is very exceptional and that the points of resemblance largely hinge upon the central changes in neurofibromatosis, a feature which in itself is rare. We feel that the similarities between tuberose sclerosis and von Recklinghausen's disease have perhaps been rather over-emphasized.

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THE GRASP-REFLEX OF THE FOOT.

BY W. RUSSELL BRAIN AND R. DESMOND CURRAN.

It is only during recent years that the phenomenon known as the grasp-reflex of the hand has become familiar, and there is still much to be learned about both its physiological and its clinical significance. Our object in this paper is to draw attention to an allied reaction in the foot.

The reflex may justifiably be called a grasp-reflex, since in all respects it closely resembles a grasp-reflex of the hand, with which it is not uncommonly associated in the same individual. By calling it a grasp-reflex we avoid the introduction of a second flexor plantar reflex which might be confused with the normal flexor plantar response.

The foot grasp-reflex in infancy.—We were first led to study this reflex by the observation, which must have been made by many others, that, though in infancy a scratch upon the sole evokes an extensor plantar response, yet plantar flexion of the toes can readily and constantly be elicited by a different form of stimulus. We have studied this reflex in fifty children of various ages. The appropriate stimulus is light pressure upon the plantar surface of the distal part of the foot including the toes; the afferent focus appears to be the ball of the great toe. A light stroking movement from the heel forwards will also evoke it. The motor response, which is unilateral, is flexion and adduction of the toes. No constant associated movements have been observed, though inversion of the foot may occur at the same time. The reflex is tonic in character, since the new posture of flexion and adduction of the toes is often maintained for a quarter or half a minute or longer. If a thin pencil be used to elicit the reflex it may be grasped by the toes and held for a quarter of a minute or more. The flexed posture of the toes may persist during movements of flexion and extension at the knee and hip, if these should happen to occur. The reflex is not elicitable during sleep.

Age incidence.—The reflex has been sought in fifty children of various ages and without disease of the nervous system, and the results are tabulated below:—

GRASP REFLEX OF THE FOOT IN NORMAL INFANTS.

Number	Age	Present	Doubtful	Absent
24	Up to 9 months	24	—	—
28	Up to 1 year	26	1	1
9	One to 2 years	5	1	3
13	Over 2 years	1 (aged 3)	—	12

It will be seen that this reflex was elicitable in all children aged 9 months or less, and in almost all aged under a year, while it had disappeared in all but one child over the age of 2 years. This child, aged 3 years, suffered from rickets, and showed both the grasp-reflex and extensor plantar responses.

We found the foot grasp-reflex absent in two infants, aged 6 months, who both suffered from bilateral pyramidal lesions and exhibited marked spasticity. One was a hydrocephalic child and the other, whom we saw through the kindness of Dr. Kenneth Tallerman, suffered from a familial cerebral degeneration. It is impossible to say whether in such cases the foot grasp-reflex had never been acquired, or had been lost through destruction of the cerebral centres concerned, or was inhibited by the spasticity.

A recent investigation by Sittig [9] of the duration of the foot grasp-reflex in normal infants has yielded results similar to our own. Up to the age of 9 months the foot grasp-reflex was present in 136 and absent in 13 children. Up to the age of 1 year it was present in 157 and absent in 35.

Association with extensor plantar response.—The presence of the grasp-reflex of the foot thus corresponds roughly with the normal persistence of the extensor plantar reflex in infancy. As in all cases the response to scratching the sole was recorded, it is possible to determine how close this coincidence is. In 23 of the 50 children the grasp-reflex was associated with extensor plantar responses, in 11 cases with flexor responses. Of 16 individuals in whom the grasp-reflex was absent, 15 showed flexor plantar reflexes and only 1 extensor plantar reflexes. It is clear from these figures and from the ages of the children in the different groups, that the grasp-reflex tends to outlast the extensor plantar reflex. In only one instance did the reverse occur.

It may be of some interest to record our observations of the behaviour of the nociceptive plantar reflex at various ages. Up to the age of 6 months this was extensor in 17 out of 18, the exception being a child 6 months old. Between 6 and 9 months 2 children

showed flexor, and 2 extensor, reflexes. Between 9 months and a year 1 out of 4 gave extensor responses, and over 12 months, 2 out of 22. Although the change from extensor to flexor reflex usually occurs at the time at which the child is learning to walk, there is no constant correlation between these events, since the reflex may be flexor in children who have not walked, or extensor in those who have done so.

The foot grasp-reflex in mongolian imbeciles.—Having observed and investigated the grasp-reflex of the foot in infants, we sought to ascertain whether it could be found in later life as a result of pathological conditions, and observed that it was fairly common in mongolian imbeciles. We have investigated the reflex in 59 "mongols" ranging from 1 to 45 years of age. It was present in both feet in 23, and in one foot only in 5. It was absent in 20 and the result was doubtful, mainly owing to difficulties of examination, in 11. Thus the reflex was obtained from one or both feet in approximately half the cases. It is illuminating to arrange these results according to the ages of the patients:—

GRASP-REFLEX OF THE FOOT IN MONGOLIAN IMBECILES.

Age of Patient	Present	Absent	Doubtful
Under 5	3	—	—
5 to 10	9	2	2
11 to 20	13	6	7
21 to 30	1	9	2
31 to 40	1	2	—
41 to 50	1	1	—

Although the grasp-reflex was found in a mongol aged 45, it was rarely observed after the age of 20. Up to the age of 20 it was present in 25 out of 42 patients, after the age of 20 in only 3 out of 17. There are two possible explanations of this fact, either that a mongolian imbecile exhibits the reflex up to a greater age than the normal individual but ultimately loses it, or that it is present only in the lower-grade mongols who are not likely to live so long as those less severely affected.

The foot grasp-reflex in cases of localized cerebral lesions.—In 1926, Schuster and Pineas [7], in their paper on forced grasping, reported one patient who exhibited a grasp-reflex in the foot as well as in the hand. This was a girl, aged 19, who three years previously had had a febrile illness followed by left hemiparesis and hemiathetosis. After describing the grasp-reflex of the hand the authors continue: "Exactly analogous changes in the toes on the left side. On the lightest touch upon the

toes or the ball of the foot there followed a maximal flexion of all the toes. If it followed a touch with a lead pencil or similar object, this was strongly grasped until an intercurrent athetoid movement of the toes released it." Professor Schuster, in a personal communication, states that he has observed a grasp-reflex of the foot in one other patient besides the one just described.

Symonds [11], in 1928, at a meeting of the Neurological Section, showed a patient who exhibited right hemiparesis, together with optic atrophy following papillœdema. This patient had difficulty in relaxing the grasp of the right hand, and when she gripped the observer's finger-tip under the toes of the right foot there was a persistent contraction, apparently of the long flexors of the toes, with flexion of the ankle. In both cases the prolonged grasp followed voluntary flexion, and Symonds reported the case as one of tonic innervation. In the discussion, however, Critchley [2] suggested the possibility of a grasp-reflex.

Sittig [10] has made a special study of the grasp-reflex both in the hand and in the foot. He has generously supplied us with notes of twenty-nine cases, most of them unpublished. In his twenty-nine cases he has found the reflex present in both hands and both feet three times, in one hand and the same foot once, in one hand alone five times, in both feet without the hands nine times, and in one foot alone eleven times. He has thus found the grasp-reflex present in the foot much more frequently than in the hand, viz., in twenty-four compared with nine patients. His cases were mostly intracranial tumours and vascular lesions. He concludes that "The grasp-reflex seems to occur also with other localization than the frontal lobe." As is the case with the hand grasp-reflex, Sittig has observed a patient in whom the onset of complete paralysis was followed by the disappearance of the grasp-reflex of the foot.

Freeman and Crosby [4], in a paper on the grasp-reflex, have reported three instances of its occurrence in the foot. All three were examples of cerebral arteriosclerosis. In one it was observed in both hands and both feet; in one, in both hands and one foot; and in the third, in one hand and one foot. Freeman [3] elsewhere likens the foot grasp-reflex in pathological states to the normal infantile reaction.

We have observed the foot grasp-reflex in the following four cases:—

(1) *Congenital choreo-athetosis.*—Ivy B., aged 2½. There was a long and difficult labour. The child was not noticed to be abnormal until it was 8 months old, when it was noticed that its right foot turned in when an attempt

was made to stand it on its feet. About the same time abnormal movements of the upper limbs were observed. At $2\frac{1}{2}$ years the child was clearly mentally defective: she was unable to speak and to sit up, and there were severe choreo-athetoid movements of the face and of all four limbs. She attempted to grasp with the hands objects presented to her, but the involuntary movements

FIG. 1.—Patient No. 1.—Foot-grasp reflex.

FIG. 2.—Patient No. 1.—Response evoked by scratching outer border of sole. Compare with fig. 1.

rendered grasping extremely difficult. There was no grasp-reflex of the hands, but a vigorous grasp-reflex was readily elicitable in both feet. The slightest contact with the flexor surface of the toes or the distal half of the sole evoked strong flexion of all the toes, which were maintained in tonic flexion for quarter

to half minute or longer. If the reflex was evoked by bringing an object such as a pencil into contact with the plantar surface of the toes, this object was grasped by the toes and held for half a minute or more (fig. 1).

The tendon reflexes were brisk and equal; the right plantar reflex was flexor and the left extensor (fig. 2).

(2) *Unverified tumour of the corpus callosum.*—Mrs. H., aged 46. There was a seven years' history of "fainting feelings," which after three years developed into convulsions. Each convulsion was followed by a prolonged state of semi-stupor. There was no papillœdema, but there was bilateral weakness with some spasticity and extensor plantar responses. Radiography showed a rounded opaque area in the fronto-parietal region, slightly to the right of the middle line. This patient for a long period showed an extremely vigorous grasp-reflex in both hands, stronger on the right than the left, and at times forced groping was present on the right side. At the same time light stroking of the sole towards the toes elicited a prolonged flexion of all the toes, which was maintained as long as the observer's fingers remained in contact with the foot. This reflex was always more readily elicited in the right foot than in the left.

(3) *Subdural hæmatoma.*—John L., aged 57, farmer, a patient of Dr. W. A. Lister, of Plymouth, and Mr. Hugh Cairns, admitted to the London Hospital August 24, 1931.

The patient enjoyed good health until May 24, 1931, when he suddenly complained of frontal headache. Subsequently headaches occurred occasionally until two weeks before admission, when they became more severe. Six days before admission became drowsy. Drowsiness varied markedly in intensity: at times he could be roused, at other times this was impossible. For four days he had been incontinent.

When examined on August 26 he was completely comatose. There was no papillœdema. He occasionally moved his limbs spontaneously and there was no evidence of paralysis of any limb. The tendon-jerks in the upper limbs and the knee-jerks were present but sluggish; the ankle-jerks and abdominal reflexes were absent. Both plantar reflexes were extensor, the right more definitely so than the left. Any moving stimulus applied to the right sole evoked a vigorous upward movement of the toe. The grasp-reflex was readily elicitable from both hands and both feet, being more vigorous in both instances on the right side. In the feet it was elicited by light pressure applied over the ball of the great toe or the flexor surface of the toes. Tonic flexion of the toes was well maintained and a pencil applied to the plantar surface of the toes was grasped and held for a number of seconds. Reflex grasping was better sustained in the right foot than in the left.

On August 28 ventriculography showed that both ventricles were displaced to the left, and there was a collection of air lying superficially to the cortex on the right side. Mr. Donald operated and carried out a right subtemporal decompression, and on opening the dura a large quantity of thin brown fluid, obviously old blood, shot out under pressure. The subdural hæmatoma was

evacuated, and although there was a temporary improvement with recovery of consciousness, the patient died on August 31 of bronchopneumonia. Post-mortem examination showed that the right hemisphere was still collapsed in the region previously occupied by the hæmatoma.

(4) *Meningioma of falx.*—A male, aged 50, was admitted to the London Hospital, under Dr. George Riddoch, with one year's history of headaches, attacks of unconsciousness and progressive dysphasia. Ten months before admission weakness of the right upper limb suddenly developed but subsequently improved, but weakness recurred seven weeks before admission. Vision had recently been deteriorating. On examination there were bilateral papil-œdema and right hemiparesis and hemiapraxia, with marked verbal dysphasia. A strong grasp-reflex was present in the right hand and also in the right foot. In the latter a scratch on the sole yielded an extensor plantar response, but a light stroking movement with the fingers along the sole from the middle towards the toes evoked strong tonic flexion of the toes. The response also occurred if the observer brought his finger-tips into contact with the plantar surface of the toes. The toes then became flexed and grasped the tips of the fingers, and this tonic flexion was so powerful that the leg could be lifted off the bed. A pencil presented to the plantar surface of the toes was similarly grasped and held.

Mr. Hugh Cairns operated on this patient and removed a meningioma weighing 55 grm. The tumour was embedded in the medial aspect of the left frontal lobe, reaching back to within about 2 cm. of the precentral gyrus. It was about 6 cm. in antero-posterior and 4·5 cm. in other diameters. It was lightly attached to the left side of the falx, just below the superior longitudinal sinus, over a small area 1 to 2 cm. in diameter.

After operation the grasp-reflex of the hand disappeared within forty-eight hours. That of the foot was not investigated for ten days, when it also was absent. There was a rapid improvement in all the other symptoms.

Physiological and Anatomical Considerations.

The foot grasp-reflex must be distinguished from the normal flexor plantar reflex. When, as in the young infant, the slightest nociceptive stimulus to the sole evokes an extensor plantar response, the normal flexor reflex can easily be excluded because it cannot be obtained. When, however, this can be elicited in an adult patient the distinction requires care. The normal flexor reflex, however, cannot in our experience be elicited by mere contact or light pressure without a moving stimulus; and in the grasp-reflex the motor response is confined to the flexors and adductors of the toes and is tonic and not phasic in character. It must also be distinguished from Rossolimo's reflex in which sudden flexion of the toes is elicited by a tap upon the ball of the foot. This reflex is a contraction of the long flexors of the toes, probably evoked

by suddenly stretching them. The grasp-reflex is obtained without displacement of the foot at any joint. Freeman and Crosby's account of their method of eliciting the reflex suggests that in two of their cases they may have obtained Rossolimo's reflex rather than the grasp-reflex.

The grasp-reflex of the foot is distinguished from the extensor thrust by its tonic character, and the fact that the motor response is confined to the flexors and adductors of the toes. When, as often happens in the infant, the foot is in a posture of dorsiflexion before the reflex is elicited, plantar flexion of the foot plays no part in the response. For similar reasons we can distinguish it from the positive supporting reaction of Magnus, and the "Widerstandsbereitschaft" of Mayer and Reisch [5]. The evidence points, in fact, to its being a specific reflex.

Like the hand grasp-reflex, it is usually associated with a lesion involving the frontal lobes, and there are indications that with a lesion near the leg areas, for example a tumour of the falx, the foot grasp-reflex may be present in the absence of the hand grasp-reflex. As in the case of the latter, it has been described with lesions in other situations, but even so both should probably be regarded as evidence of disturbance of function of the prefrontal region.

The similarity of the foot grasp-reflex to the hand grasp-reflex and their association in the same patient naturally leads us to look for a similar interpretation of both. Adie and Critchley [1] drew attention to the resemblance between the pathological hand grasp-reflex and the normal character of reflex and spontaneous grasping in infancy. A similar analogy holds good of the foot grasp-reflex which can also be studied in any infant.

These reflexes appear to be elicitable only when there is a deficit of certain paths which originate in the frontal lobes and which may be normally undeveloped as in the infant, abnormally undeveloped as in the mongolian imbecile, or destroyed by disease. The precise course of these paths has recently been investigated in the case of the hand grasp-reflex by Schuster and Casper [8]. They report the pathological findings in a number of cases, in three of which the brains were cut in serial sections. They conclude that the hand grasp-reflex is a release phenomenon, and is normally inhibited by impulses which originate in the first frontal convolution and the gyrus fornicatus and are brought to bear upon the origins of the pyramidal tract in the precentral convolution. Each pyramidal tract is believed to be in this respect under the control of both frontal lobes, the inhibitory fibres from the opposite

hemisphere crossing in the corpus callosum to join those from the ipsilateral hemisphere. In order that the grasp-reflex may appear it is necessary that the fibres from both frontal lobes shall be interrupted. The lesion in most cases is so situated as to involve the first frontal convolution on one side and the adjacent half of the corpus callosum, thereby interrupting the fibres from the opposite side.

The commonest lesions which are appropriately situated to allow reflex grasping to occur are intracerebral tumours involving the medial aspect of the frontal lobe, tumours of the corpus callosum and of the falx, and cerebral softening due to thrombosis of branches of the anterior cerebral artery. Diffuse cerebral degeneration involving the frontal lobes may produce the same effect. The occurrence of bilateral hand and foot grasp reflexes in our third patient who had a subdural hæmatoma in the right fronto-parietal region cannot be explained as a result of direct pressure by the hæmatoma upon the medial aspect of the frontal lobes, but was probably due to transmitted pressure, the displacement of both hemispheres, clearly indicated in the ventriculogram, causing these areas to be compressed against the falx.

These anatomical considerations, however, do not afford an explanation of the nature of the grasp-reflex, nor do they explain why the human infant exhibits reflex prehension with its toes. Prehensile toes naturally suggest the anthropoid apes and monkeys, and we therefore studied the palmar and plantar reflexes of such of these animals as were accessible at the Zoological Society's Gardens, facilities being kindly given us by Dr. Vevers and the head keeper of the monkey house. We examined one chimpanzee, one orang-outan, six monkeys and one lemur. Only one showed a hand grasp-reflex, a young pig-tailed monkey, 12 months old. All the monkeys showed well-marked grasping in the feet in response to moving contact, but this was not evoked by simple contact or by pressure. Neither of the anthropoid apes showed a grasp-reflex in the feet. The prehensive functions of the adult monkey's foot are activities of a highly specialized character. The grasp-reflex in man seems simpler and more rudimentary, an activity of a lower order. The infant monkey, however, exhibits true reflex grasping. As soon as it is born it is slung beneath the mother's belly, clinging to her flanks with its hands and feet and receiving no support whatever from her. Though only a day or two old, it holds on while she jumps from bough to bough, and does not leave her until it is weaned. We have observed a number of infant monkeys, some within a few days of birth, and the tenacity of their grasp of the mother is astonishing.

Richter [6] has recently investigated the hand grasp-reflex of the infant monkey. He found that it was much stronger than in the newborn human infant, one of the monkeys hanging for over thirty-three minutes by one hand alone. The reflex hand and foot grasps of the infant monkey offer a phylogenetic explanation of reflex grasping.

The foot grasp-reflex of the mongolian imbecile should not be regarded as indicating that the mongol is in any peculiar sense simian. Anatomical evidence strongly suggests that mongolism is due to a check in development during the third month in fœtal life, and that the characteristic mongolian traits are fœtal rather than simian. At least they are simian only in the very general sense that the human fœtus in its development to some extent recapitulates human evolution. It is not surprising that the mongol should therefore exhibit a reflex characteristic of early human infancy.

SUMMARY.

(1) A grasp-reflex of the foot similar to that of the hand is described.

(2) The foot grasp-reflex is normally present in the human infant during the first year of life, and usually persists somewhat longer than the extensor plantar reflex.

(3) The foot grasp-reflex is elicitable in approximately 50 per cent. of mongolian imbeciles.

(4) It may also occur as a result of lesions of the frontal lobe.

(5) A homologous foot grasp-reflex is present in the infant monkey.

We are indebted to Dr. George Riddoch and Mr. Hugh Cairns for kindly allowing us to investigate their cases, and to Dr. S. Behrman for the photographs illustrating Case 1.

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GLOSSOPHARYNGEAL NEURALGIA.[1]

BY W. S. KEITH.

As late as 1926 it was said by Dana of the glossopharyngeal nerve, "It has no tic or palsy or algia . . . it receives only disregard and aloofness from surgeons and clinicians." This statement appears in a discussion of glossopharyngeal neuralgia by Stookey, and is reproduced here to emphasize how recently this condition was described.

The earliest reports of glossopharyngeal neuralgia have been fully discussed by Dandy, Stookey and others. Weisenberg, in 1910, was the first to describe the symptoms of irritation of the glossopharyngeal nerve, in a case of tumour of the cerebellopontine angle. In 1920, Sicard and Robineau reported three cases each of which was probably true glossopharyngeal neuralgia. In 1921, Harris described "a rare form of paroxsymal neuralgia or tic douloureux which affects the glossopharyngeal nerve." Since this time reports of this disease by Doyle, Adson, Harris, Albright, Singleton, Goodyear, Dandy, Stookey, Fonio, Hansel, Bailey, Brock and Martin have appeared. Dandy collected and published in tabular form detailed information in twenty cases. Seventeen additional cases are here recorded in tabular form and three of these are reported in detail.

Case 15.—Mrs. W. J. B. Aged 44. In 1911 while eating some fruit this patient was suddenly seized with a sharp pain in the left side of her throat. She thought she had taken a piece of glass into her mouth. In 1912 she had her left tonsil removed with complete relief from pain for three years. Between 1915 and 1922 she had about six painful attacks lasting up to three or four months each. The pain was at its worst in early spring but disappeared in summer. Sweet things such as honey, syrup or fruit, and sour things such as tomatoes, pickles or vinegar, always brought on an attack. She was unable to take solids or cold liquids when most subject to pain and at these times, chewing, speaking or even stooping over might initiate an attack. When subject to attacks she would remain in bed and would refuse all nourishment. She salivated freely and would let the saliva run out of her mouth from fear of swallowing it. The attack itself came suddenly, but sometimes there were one or two warning throbs. The sensation was described as being like a knife

[1] From the Neuro-surgical Service of the Toronto General Hospital.

Case number	Author and year	Age and sex	Duration of pain	Nature of pain	Location and radiation of pain	What induces pain	Duration of paroxysms	Pain in ear
1	Singleton 1926	F. 45	2 years	Intense suffering	Left side of throat radiating to side of neck and to ear	Swallowing or talking	..	+
2	Singleton 1926	F. 46	Several years	Severe paroxysmal pain	Posterior part of tongue, tonsillar region, deep in neck below the angle of jaw	..	..	..
3	Albright, 1926	F. 66	Few months	Severe spasmodic	Began in throat and radiated to and was worst in ear. Later around ear and over side of face. Was in teeth too	Swallowing, taking a breath, talking	Moment or two	+
4	Hansel .. 1928	F. 23	2 years	Excruciating and lancinating	Left side of pharynx radi ating to ear	Swallowing, chewing, talking	Few seconds	+
5	Hansel .. 1928	F. 47	5 years	Paroxysms of excruciating pain	Right side of pharynx radiating to ear	Eating and talking	30 to 60 seconds	+
6	Hansel .. 1928	F. 61	18 months	Severe lancinating pains	Right side of throat radiating to ear	Chewing, swallowing, drinking cold water	Few seconds	+
7	Hansel .. 1928	M. 52	10 years	Excruciating and lancinating pain	Left side of throat and neck radiating to ear	Talking chewing, swallowing	30 seconds	+
8	Hansel .. 1928	M. 60	2 years	Stabbing, excruciating pain	Left side of pharynx radiating to ear (tragus)	Talking, swallowing, chewing	Few seconds	+
9	Fonio .. 1928	M. 75	..	Very intense pain	Right tonsil and right side of throat radiating to ear and towards eye	Speaking, chewing, swallowing	Several seconds	+
10	Stookey . 1928	M.	..	Very frequent and severe attacks of pain	..	..	..	..
11	Brock .. 1931	M. 61	Few months	Severe paroxysms	Right side of tongue and tonsil and radiating to ear	Swallowing or protrusion of tongue	Transient	+
12	Bailey .. 1931	F. 59	6 months	Boring pain	Left tonsil and left side of throat radiating to ear	Swallowing	..	+
13	Bailey .. 1931	F. 36	6 years	Sudden excruciating pain	Base of tongue and left side radiating to ear	Swallowing	Transitory	+
14	Martin .. 1931	M. 61	8 years	Severe stabbing and burning	Pain began in ear and radiated to throat. Pain most severe in ear	Swallowing or talking sometimes	Few seconds	+
15	Keith .. 1932	F. 44	12 years	Stabbing and twisting	Side of throat and tonsillar area. Later radiating deep in ear and neck	Swallowing, especially sweets or sour things	Less than 30 seconds	+
16	Keith .. 1932	M. 45	3 years	Agonizing sudden pain	Side of throat and jaw	Swallowing, drinking	20 seconds	+
17	Keith .. 1932	F. 60	14 years	Boring pain	Deep in ear and behind and in lobule—radiating somewhat to throat	Swallowing	½ to 3 minutes	+

Pain uni-lateral	Periods of remission from pain	Trigger zone	Any associated disease	Treatment	General remarks
+	+	..	None found	Avulsion of glossopharyngeal nerve in the neck	During attack a finger pressed over ear. The other hand pressed against side of neck
+	+	..	..	Alcohol injection of Gasserian ganglion with total anæsthesia. No relief	Later in another Clinic the root of the 5th nerve was divided. No relief. Post-operative diagnosis: Glossopharyngeal neuralgia
+	+	+	None found	Alcohol injection of Gasserian ganglion without relief. Advised operation on glossopharyngeal nerve	Greatest severity of pain was "right in the ear." Cocaine anæsthesia of right tonsillar region temporarily stopped the spasms
+	+	..	None found	Wisdom teeth removed	..
+	+	..	None found	*Nil*	..
+	+	..	None found	Refused operation	..
+	+	..	None found	Operative treatment advised	Had had operation for lung abscess and had diabetes
+	+	..	None found	Patient did not wish operative treatment	..
+	+	..	Aneurysm of common carotid artery	Three operations on aneurysm. Then avulsion of glossopharyngeal nerve in neck	..
..	..	..	..	Intracranial section of glossopharyngeal nerve	Feeling of dryness of the mouth on the same side as the pain
+	..	Side of base of tongue	None found	Novocain and alcohol injection three times. 9 months-1 year apart. Relief each time	Had abscess in right pyriform fossa three years before. Died. No autopsy
+	..	..	Carcinoma of the larynx	Intracranial section of glossopharyngeal nerve by Dr. Davenport	Complete relief from operation. Pain later appeared on the other side and patient died two months after operation
+	..	..	None found	Intracranial section of glossopharyngeal nerve	Removal of teeth and injection of alcohol into mandibular nerve gave no relief
+	+	..	None found	Phenazone and gelsemium	Left side of throat felt dry. Increased flow of saliva with spasms
+	—	..	None found	Avulsion of glossopharyngeal nerve in neck and division of pharyngeal branch of vagus	Has had severe pain at times since operation
+	+	Between tonsil and tongue	None found	Avulsion of glossopharyngeal nerve in the neck	Cocaine anæsthesia of left tonsillar region temporarily stopped the spasms
+	+	..	None found	Avulsion of glossopharyngeal nerve in the neck	..

stabbed into and twisted in the side of the throat. She stated that the worst spasms forced her to her knees so that she prayed she might die before another attack came. The pain never lasted longer than half a minute. It seemed to be inside the throat in the region of the root of the tongue on the left side and just below the angle of the jaw deep in the left side of the neck. In the last two or three periods of attacks the pain had often radiated deep into the left ear.

On physical examination the patient was found to have a colloid goitre of moderate size. No other abnormalities were found. X-rays of the teeth were reported normal. A diagnosis of glossopharyngeal neuralgia was made.

Operation.—March 21, 1923. Under intra-tracheal ether anæsthesia an incision was made below the left mandible. The glossopharyngeal nerve was exposed and divided and the proximal end was avulsed. The pharyngeal branch of the vagus nerve was divided. On March 22 the pain was gone. On April 2 the patient was discharged completely relieved of symptoms. In December, 1924, the same pain returned. One series of spasms at this time was the worst she had ever experienced. In the springs of 1925, 1927 and 1929, she had similar attacks lasting over periods of from one to three months. With the exception of the severe bout mentioned above, the pains since operation have been less severe than those before.

Case 16.—Mr. W. H. E. Aged 45. In March, 1923, the patient awoke one night with pain in the left side of his throat. It disappeared before morning. In March, 1924, while drinking cold water he was suddenly seized by a terrific pain in the left side of his jaw and throat. He stated that it felt as if he had been hit by a base-ball bat on the angle of his jaw. There were no more attacks until October, 1925, when a more severe agonizing pain occurred in the same place very suddenly while drinking cold water. From this time he suffered frequently from pains of varying severity until he presented himself for examination in January, 1926. There were intervals of as long as a month between major attacks. These attacks came without any warning, sometimes while reading but usually while talking, eating or drinking. Sneezing or coughing did not bring them on. They lasted about twenty seconds and were so severe that he had great difficulty in localizing them. However, as each pain passed off the region of the left tonsil and back of the tongue on the left side remained sore. He also noted that during the severe attacks he had pain immediately in front of the external auditory meatus. This latter pain seemed to radiate toward the temporal region. He complained of two types of pain between the major attacks. One was described as of an oat husk caught between his left tonsil and tongue and from here small, shooting and quick pains radiated. They kept him in fear of the so-called big pain. The other unpleasant sensation was a dull ache as if a very heavy weight were suspended from the affected parts. The patient seemed to be most subject to pain in the spring and autumn. He had small pains only in the hot weather. In January, 1926, he stated that there was pain in the two left posterior lower teeth with some insignificant radiation to the upper lip and eyelid. He once got relief by having the painful area swabbed with cocaine.

On examination it was observed that there was a "trigger" spot between the left tonsil and the tongue, indeed, the patient dropped to the floor with severe pain when touched on this spot. When asked to cover the painful area however, he placed his hand over the whole of the left mandible. At this time a note was made that the condition was probably not glossopharyngeal neuralgia. General physical examination was entirely negative. A diagnosis of neuralgia of the third division of the trigeminal nerve was made.

On January 16, 1926, alcohol injection of the left mandibular nerve was done. On March 8, there was no anæsthesia in the mandibular area, but the injection had given relief. The patient dreaded the return of pain at a time when it would be almost impossible for him to come for operation, so partial division of the sensory root of the fifth nerve was advised.

Operation.—March 22, 1926. Under intratracheal ether, the usual approach through the middle fossa to the Gasserian ganglion was carried out. About two-thirds of the sensory fibres were avulsed. The motor root was left intact. On April 5, 1926, he returned to his home. He had been free from pain since the alcohol injection. In January, 1928, the patient returned because of stabs of pain in the original spot. There was complete loss of sensation in the whole left trigeminal area.

On February 13, 1928, the following note was made: For three or four days the patient has been lying in bed, refusing to swallow anything. Some food became lodged between his tonsil and tongue and nearly sent him crazy. The pain starts in the tongue and anterior pillar of the tonsil and goes down just below the angle of the jaw and up just in front of the ear. Spasms last about twenty seconds. A diagnosis of glossopharyngeal neuralgia was made.

Operation.—February 14, 1928. The glossopharyngeal nerve was exposed through an incision below and behind the mandible. It was avulsed from above and below. About two and one-half inches of the nerve were removed. Four hours after operation it was impossible to produce the old pain by any form of stimulation. In February, 1929, it was noted that the palate elevated in the midline. There was no pain, but there was anæsthesia in the posterior part of the tongue on the left side and around the left tonsil.

The patient reported that during the winter of 1929-1930, he had several jerking feelings without pain, in the left side of his face and head. In October, 1930, small pains radiating from the "oat husk" area into his throat and tonsil region began again and caused him concern all winter. He stated that he would rather die than have the severe attack again.

Case 17.—Mrs. C. K. Aged 60. In 1916, for four or five days the patient had her first attacks of pain in the region of the right ear. In 1917, and in 1922, respectively, the pains recurred for from four to six weeks each time. The pain was referred to the external auditory canal, the lower one-third of the pinna and the area immediately behind the head of the mandible. It was brought on chiefly by drinking cold liquids, but swallowing was sufficient to induce an attack at the worst times. The severe pain lasted one to three minutes, but a burning sensation lingered for some five to ten minutes.

Beginning about September, 1930, the patient had occasional slight "warning" pain in the same place. In January, 1931, she caught a cold and while she was recovering in February the pains returned worse than ever. A severe spasm was described as follows: For about three minutes or more she had a sensation as if an auger were being bored into her right ear. The boring then stopped and a red-hot rod was left in the hole for five to ten minutes. The spasms were brought on by swallowing. She stated that for as long as ten days at a time she had been unable to swallow anything but small amounts of warm fluids. Yawning, sneezing and coughing also induced spasms. During the attacks there was some pain in an indefinite area in the region of the right tonsil, but this was apparently insignificant in comparison with the more superficial pain. In May, 1931, she had a nerve in the right side of her face injected through her nose with some temporary relief. Two weeks later some bone was removed from inside her nose and another injection was done. The injection was repeated a fortnight later.

On examination, the patient was thin and appeared to be about 65 years old. The blood-pressure was 190/90. When asked where her pain was located, she pointed to the region between the head of the mandible and the mastoid, and very gingerly grasped the pinna behind and below the external auditory meatus. She would not allow the region of the right ear to be touched, because the least manipulation would bring on a spasm. No "trigger" spot could be found inside her mouth. Gagging always induced a spasm. The spasms were not as bad as they had been, and lasted not more than one-half to one minute. During the attack she cried and moaned, but did not touch the painful area. Her head was held turned slightly to the left, and she resented movement in any direction. Movements were very slow and deliberate. Digital pressure or pinching of the skin anywhere within two inches of the external auditory canal produced a spasm. Even pressure on the clavicular tendon of the sternocleidomastoid muscle caused severe pain. There was some hypæsthesia in the region of the second division of the right trigeminal nerve. There were no other neurological findings.

A provisional diagnosis of glossopharyngeal neuralgia was made, though it was felt that some of the fibres of the vagus might be involved as well.

Operation.—July 10, 1931. Incision was made below the ramus of the right mandible. The glossopharyngeal nerve was exposed and divided. The proximal end was avulsed, about one and one-half inches of the nerve being removed. The distal end was buried in the digastric muscle. Four hours later one could manipulate the pinna and neighbouring parts and produce only pain referred to the incised wound.

On July 20, 1931, the patient was able to eat, drink, talk, sneeze and cough as she pleased, and without pain. There was no tactile sensation on the front of the soft palate on the right side. There was absence of taste for sugar and salt on the posterior one-third of the right side of the tongue. The palate was elevated in the midline, but it seemed to hang a little lower on the right side than on the left. There was no disturbance of tactile sensation in the region of the right ear.

The term tic douloureux has for a long time been synonymous with a certain type of neuralgia of the trigeminal nerve. In view of the marked similarity between cases of glossopharyngeal neuralgia and the much more common trigeminal variety, and indeed their not infrequent confusion, it seems reasonable to use tic douloureux as a generic term to include both conditions.

The diagnosis of tic douloureux rests upon the history of the disease and observation of the attacks. Abnormal physical findings are almost always absent. It follows, therefore, that the two anatomical types of tic douloureux must be distinguished by analysis of the history. Observation of the attacks may be an aid in some cases. For these reasons it is justifiable to consider in some detail all the reports of glossopharyngeal neuralgia.

Tic douloureux of the glossopharyngeal nerve usually occurs after 40 years of age. The paroxysms of pain are always very severe and of brief duration. Dandy suggests that the pain is usually more severe and of shorter duration than in trigeminal neuralgia. The pain in practically every case is induced by swallowing or some form of movement of the fauces, pharynx or tongue, although it may occur spontaneously as well. In every case the pain is unilateral except where an associated neoplasm has crossed to the other side. In this latter instance the character of the pain is likely to have changed. It is probable that in every case unassociated with a neoplasm there have been one or more periods of spontaneous remission from pain. This observation, however, is not mentioned in all case reports. One remission of eight years in Case 17 is the longest on record. The pain nearly always begins in the throat, in the region of the tonsil, or in the base of the tongue. The place of origin of the pain is nearly always the seat of its greatest severity. In most cases the pain begins and is most severe in the throat. In Cases 14 and 17 the pain began in the ear and was most severe in the ear. In Case 3 the pain began in the throat but was most severe in the ear.

Radiation of pain to the ear at some stage in the disease nearly always occurs. It is usually described as being deep in the ear. The anatomical explanation of this pain deep in the ear lies in the fact that the glossopharyngeal nerve contributes a branch called Jacobsen's nerve to the tympanic plexus. Dandy makes the statement that there is no external sensory supply by the glossopharyngeal nerve. However Ramsay Hunt collected anatomical, embryological and experimental evidence which shows that the glossopharyngeal nerve through a small

twig to the auricular branch of the vagus nerve contributes to the supply of the posterior part of the tympanum, the posterior wall of the auditory canal, part of the concha and a strip on the postero-medial surface of the auricle, and the immediately adjacent mastoid region. Entirely new evidence of the superficial distribution of glossopharyngeal fibres in this area is to be found in the fact that this was the exact distribution of pain in Case 17, and that part of this area was the chief seat of superficial pain in Case 14. In Case 10 no sensory loss could be demonstrated in this area after intracranial section of the glossopharyngeal nerve. This is due to the fact that this small area is completely overlapped by other nerves of the region. Additional evidence of the contribution of the 7th, 9th, and 10th cranial nerves to the supply of this superficial area is to be found in Ramsay Hunt's observations on herpes zoster of these nerves and in an interesting case reported by Neve; this patient had herpes zoster of the left half of the soft palate with pain behind and below the left ear and down the left side of the neck. He considered this to be a case of herpes zoster of the glossopharyngeal nerve.

In a few cases the pain seems to overflow the area supplied by the glossopharnygeal nerve and spread down over the upper cervical segments or up into the trigeminal region. It would appear that this usually occurs late in the history. In Cases 1 and 17 there was some pain down the side of the neck. In Cases 3, 9 and 16 the pain radiated somewhat into the trigeminal area, into either temporal or mandibular regions. Occasionally the teeth are complained of. In Case 16 the patient had some pain in his back lower teeth, and in one of Dandy's cases the patient felt as if his teeth "would jump out of their sockets."

Two factors contribute to the patient's difficulties in describing the pain. In the first place, whereas the glossopharyngeal nerve is almost entirely distributed to deep structures, there may be an unconscious tendency for some patients to interpret their pain in terms of superficial structures. In the second place, the pain is often so severe that the patient has difficulty in localizing it. It is probable that both these factors were present in Case 16.

In Cases 10, 13 and 14 there was a sensation of dryness in the painful side of the throat. In the latter case there was also increased flow of saliva in the paroxysms. In some instances increased salivation may be more apparent than real, owing to accumulation of saliva through fear of swallowing. "Trigger" spots and marked tenderness, or rather perhaps fear of touching the part, seem to be different degrees of the

same thing, and are well marked only when the patient is most subject to attacks. The seat of the worst pain is usually that of the "trigger" spot. In one of Dandy's cases the patient found that he could swallow with impunity for a few moments following a paroxysm. As in trigeminal neuralgia, patients sometimes adopt certain attitudes or movements during the paroxysms. These include placing tip of index finger in the auditory canal and wiggling it around, one finger pressed to the ear and the other hand to the neck, grasping the table, leaning forward to let saliva run from the mouth, &c.

Of thirty-seven cases of glossopharyngeal neuralgia reported, two had carcinoma of the tonsil, one had carcinoma of the larynx, one had an aneurism of the internal carotid artery, and one had a tumour of the cerebello-pontine angle. The incidence of associated disease, therefore, is much higher than in trigeminal neuralgia, and this fact should always be remembered when the diagnosis of glossopharyngeal neuralgia is made.

Treatment.—It has long been established that section of a sensory root proximal to its ganglion results in permanent loss of sensation in the region supplied by the nerve. This is the only attack on the nerve which assures that the loss will be permanent. Intracranial section of the glossopharyngeal nerve, as advocated by Adson and carried out by Davenport (Case 12), Dandy and Stookey, is, then, the only sure method of permanently relieving the patient's pain. A case recorded by Adson and No. 15 of this series are known to have had recurrence of pain following avulsion of the nerve in the neck. Indeed, it was this former case which prompted Adson to work out his intracranial operation. It seems certain that Stookey's prediction that section of the dorsal root will prove the only successful procedure for glossopharyngeal neuralgia will be vindicated. Avulsion of the nerve in the neck may occasionally be indicated when the operative risk is great or where the diagnosis is in doubt. There seems to be a general agreement that there is almost no subjective disturbance in the throat following either operation. There must be a very few instances, such as Case 14, in which glossopharyngeal neuralgia is so much relieved by drugs that operative interference is unwarranted.

According to Dr. K. G. McKenzie, however, it is questionable if intracranial section of the nerve has sufficient advantage over extracranial section to justify what is undoubtedly a more formidable procedure. Extracranial avulsion of the nerve immediately stops the pain of a true glossopharyngeal neuralgia. The operation is an easy one as it is a

simple matter to palpate the styloid process, and from this landmark dissect out the stylopharyngeus muscle and locate the glossopharyngeal nerve in its characteristic relationship to the muscle. He believes it is unlikely that regeneration of the nerve will take place if the distal part of the nerve is sutured into fascia or muscle with silk, as in Case 17.

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SYPHILITIC HYDROCEPHALUS IN THE ADULT.

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FROM the frequency with which the basal meninges are affected in the secondary and tertiary stages of syphilis one might expect that syphilitic hydrocephalus would be common; and undoubtedly the milder forms of hydrocephalus in infants are often due to syphilis. Thus Jeans and Cooke found hydrocephalus in one-third of the syphilitic children in their clinic in whom the nervous system was in any way affected. The hydrocephalus was always of the communicating type and was never extreme. Ibrahim is of the same opinion; in his own experience the greater degrees of hydrocephalus are practically never due to syphilis, but he found occasional references in the literature to syphilitic cases of non-communicating hydrocephalus in which the heads were very large. On syphilitic hydrocephalus in the adult, however, the literature is strangely silent. Most textbooks make no reference to it; even Jakob, who devoted more than 250 pages to the pathology of cerebral syphilis and described gummatous meningitis with a wealth of detail, does not mention it. Gowers, Oppenheim and Nonne are equally silent, although Oppenheim's description of the symptomatology of basal gummatous meningitis resembles very closely that found in our hydrocephalic cases. Collier and Adie, in Price's "Textbook of the Practice of Medicine," seem to be the only authors who draw attention to acquired syphilis as a cause of hydrocephalus. They mention three post-mortem cases, in which however there was "no obstructive lesion by which ventricular distension could have arisen mechanically." It would therefore appear to be a rare cause of death.

We have attempted to estimate its incidence by an examination of the post-mortem records at the National Hospital, Queen Square. During the past twelve years, among 997 autopsies at this hospital, there were twelve cases of hydrocephalus. Of these two were congenital and in two the condition followed meningococcal meningitis. In three the ætiology was doubtful; two may have been syphilitic as there was considerable arachnoiditis, but beyond this there was no definite

evidence. In five the evidence of syphilis was considered sufficient to warrant their inclusion in this paper. In two of these the immediate cause of death was a decompressive operation undertaken to save the patient's eyesight. In addition two patients who had been under treatment for basal gummatous meningitis in the hospital died suddenly at home, and were the subjects of inquests from which we were fortunately able to collect pathological material. Thus death was directly due to hydrocephalus in five of our cases.

During the same period the post-mortem records include six cases of syphilitic vascular disease, three of other forms of cerebral syphilis, and thirty-two cases of general paralysis. If these figures were trustworthy, syphilitic hydrocephalus in the adult would appear to rank along with syphilitic vascular disease as a cause of death, but the figures are invalidated by the fact that cases of cerebral hæmorrhage of syphilitic origin are usually either admitted to general hospitals or die at home, whereas cases of more subacute onset and obscure nature, especially those associated with papilloedema or blindness, would be sent to a special hospital for nervous diseases.

There appears to be no doubt, however, that syphilitic hydrocephalus is definitely more common at the present day than the form of gummatous meningitis associated with the presence of isolated large gummata. Of this condition no fatal case is found in the records of the past twelve years, and only two cases were subjected to operative treatment during that period. On the other hand if we refer to such neurological classics of the pre-Wassermann era as Gower's Manual and the earlier editions of Oppenheim's textbook we gain the impression that isolated gummata "varying in size from that of a nut to that of a walnut" (Gowers) are among the commoner lesions of cerebral syphilis. Oppenheim it is true emphasizes the frequency with which gummatous meningitis assumes a more diffuse form, but in his experience also large gummata were not uncommon.

The post-mortem records at the National Hospital for the years 1893 to 1914 inclusive contain ten cases of cerebral gumma. In one of these the chief lesion and the direct cause of death was hydrocephalus of the non-communicating type associated with numerous meningeal gummata the size of peas. This was the only fatal case of syphilitic hydrocephalus during this period. It is probable, however, that the milder forms of hydrocephalus, especially those of the communicating type, are not uncommon, but are more amenable to treatment; and the symptoms produced by distension of the ventricles and increased intra-

cranial pressure are often attributed, as by Oppenheim, to diffuse involvement of the meninges. This supposition is confirmed by the descriptions, in the older literature on acquired hydrocephalus, of lesions such as chronic meningitis and granular ependymitis which suggest a syphilitic ætiology.

It seems, therefore, that syphilitic hydrocephalus in the adult is not so rare as to be unimportant, and our experience indicates that, especially in the more acute cases of the non-communicating type, there is still a risk of mistaken diagnosis and faulty treatment. A record of seven cases in which post-mortem evidence is available may, therefore, be of value both in giving an indication of the symptomatology of the condition and in establishing its pathological basis.

Summary of Case 1.

A woman of 39 presented the symptoms and signs of increased intracranial pressure. She also had minor, and later, major epileptiform seizures, during one of which she died. The history suggested an old syphilitic infection but no serological evidence of this was available, the blood Wassermann reaction being negative. Pathologically the condition was one of hydrocephalus due to obstruction of the foramina in the fourth ventricle by basal meningitis. Numerous miliary gummata were present over the pons and medulla.

Case 1.—M. R., a married woman, aged 39, was admitted to Hospital on June 18, 1928, under the care of Dr. Grainger Stewart. She complained of persistent headaches for the past five years, accompanied during the last ten months by vomiting. The headaches began on waking in the morning and were localized to the frontal and occipital regions. Occasionally double vision occurred on looking upwards and to the right. For about ten months hissing noises had been heard in the right ear accompanied by giddiness and a tendency to fall to the right side. Smells had recently become unpleasant, e.g., bread smelt like "mouldy cheese," a lighted cigarette like "burning rags."

Family history.—There was no evidence of syphilitic infection except that of her four children the third, a boy, aged 15, had "osteomyelitis" in "all the limbs" and was blind in the left eye. On examination the patient was mentally alert and co-operative. Her memory was good and she had no delusions or hallucinations. Speech was normal. The edges of both optic discs were blurred; in the right there were 2·5, and in the left eye 3·5 dioptres of swelling and in addition some fine streaky hæmorrhages in the retina. The pupils were equal, regular in outline and reacted to light and on convergence. No diplopia could be demonstrated. There was partial bilateral ptosis and the

patient complained that upward movement of the eyes made her feel sick. Very fine rapid horizontal nystagmus was present on full lateral deviation of the eyes, and was more marked in the left eye on looking to the right side. The corneal reflexes were diminished on both sides. There was a fine tremor of the outstretched hands and motor power was better in the left arm than in the right. The deep reflexes were grossly exaggerated but equal on the two sides. The left upper abdominal reflex was weaker than the right; both lower abdominal reflexes were absent. The plantar response was flexor on the right side and doubtful on the left. The gait was normal, but on looking upwards there was a tendency to fall backwards. The heart was not enlarged and the blood-pressure was normal (125 systolic, 80 diastolic). The liver and both kidneys were palpable. The Wassermann reaction in the blood was negative. The cerebrospinal fluid was not examined.

Whilst in hospital the headaches and vomiting became more severe. The knee and ankle jerks became brisker on the left side and the left plantar response became definitely extensor. A series of minor seizures without loss of consciousness or convulsions occurred and were followed a few days before death by definite epileptiform seizures with temporary loss of consciousness and rigidity of the limbs with the arms adducted and extended across the front of the trunk (c.f., tonic cerebellar fits). Two attacks of tetany, each lasting half an hour, occurred on July 18. The patient died on July 31, during an epileptiform seizure.

A post-mortem examination was made about twenty-four hours after death. The brain and cervical cord only were removed. On removing the calvarium, which was irregularly thickened, the convolutions appeared flattened. There was a moderate pressure cone. No tumour was visible on the surface of the brain. The membranes round the foramen of Magendie were matted together so that it needed considerable dissection to open into the fourth ventricle, which was then found to be dilated. There was also a dilatation of the third and lateral ventricles, though not of great degree. Over the front of the pons on the left side of the basilar artery were two sessile whitish cushions, about 2 mm. thick, in the pia arachnoid. The pia arachnoid was also thickened in both Sylvian fissures, depressing the brain tissue under it. Section of the brain at these areas, however, revealed no softening. The pituitary fossa was shallow, but the pituitary body was quite rounded and showed no evidence of compression. Similar arachnoidal thickening was found over the upper part of the cervical cord where little knots, several millimetres in thickness, were seen.

Histologically the condition was one of syphilitic meningitis. The small gummata over the pons were masses of thick fibrous tissue infiltrated with small round cells; in places they were necrotic, but not definitely caseous. The meninges were everywhere infiltrated with lymphocytes, and over the pons and upper part of the medulla contained numerous small gummata. Within these and also lying in clusters among the small infiltrating cells were many multinucleated giant cells in which the nuclei were distributed throughout the

cytoplasm. There was much perivascular infiltration of the meningeal vessels in this region, and many vessels showed hyaline degeneration of their walls. Round the upper part of the medulla and to a less extent over the ventral surface of the pons there were outgrowths of neuroglia through rifts in the pia mater. These were more numerous and larger than those in Case 4, but the neuroglial feltwork composing them contained fewer differentiated neuroglial fibrils; these were seen chiefly near the outer edges of the tufts. Numerous small tufts of neuroglia covered by ependyma projected into the fourth ventricle, which in its lower part appeared almost full of newly-formed neuroglial tissue.

Over the cervical cord the lymphocytic infiltration extended along the nerve-roots as well as into the walls of the meningeal vessels but it did not involve the walls of the vessels in the cord itself. The Weigert-Pal method revealed definite pallor of the column of Goll in addition to a generalized pallor of the periphery of the cervical cord. The nerve-cells in this region appeared healthy. No abnormalities were detected in sections from the frontal cortex or mid-brain, and except for perivascular infiltration of the vessels under the floor of the fourth ventricle the pons and medulla appeared normal. Perivascular infiltration with small lymphocytes was present round many vessels in the globus pallidus but not in other parts of the basal ganglia.

Summary of Case 2.

A man, aged 30, suffered from headache, "vaso-vagal" attacks and an unsteady gait. His signs were those of a lesion in the fourth ventricle. The cerebrospinal fluid provided evidence of syphilis, and treatment was instituted. The patient died suddenly after a fit in his sleep. Pathologically internal hydrocephalus was present and numerous miliary gummata were discovered in the cerebellum.

Case 2.—J. E., a married man, aged 30, was admitted to hospital on September 12, 1929, under the care of Dr. Symonds. He complained of headache, "pins and needles" in the hands, fainting attacks and transient double vision. All the symptoms had been present for about three months. The headache was worse in the morning and the pain often extended to the back of the neck. The patient did not fall during or after the fainting attacks, but had noticed that his gait had become unsteady and his speech less distinct. In other attacks, which had occurred only at night two or three times a week for the previous three months, he felt "cold all over," broke out into a cold sweat and was unable to move a muscle: his mouth twitched on one side, and for about ten minutes he was unable to move a finger or to speak; in attempting to do so he only mumbled. There was no history of syphilitic infection. His wife had had no children, but one miscarriage.

On examination, the patient's speech was monotonous and rather indistinct. His memory and intellect were good. The pupils were equal, regular, and

reacted to direct and consensual light and on convergence. The optic discs were normal. The tongue was protruded to the right, and showed deep markings on its upper surface. Motor power was good, and the reflexes were unchanged. Sensation to pain and light touch was normal. Vibration was less appreciated on the right hand than on the left, was lost on the chest below the level of the nipple, felt over both great trochanters, but was absent below this level. His gait was unsteady with eyes closed, and he deviated to the right in walking. He was unable to stand on either leg alone. The size of the heart was within normal limits. The systolic blood-pressure was 130, the diastolic 70.

Cerebrospinal Fluid: Cells 260 per c.mm. chiefly small lymphocytes, 10 per cent. large mononuclears, 1 per cent. polymorphonuclears: total protein, 0·125 per cent.: Nonne Apelt positive, Pandy strongly positive: Lange 0001112110: Wassermann reaction positive, 4444 in fluid, 4444 in blood.

Whilst in hospital, he had several attacks of vomiting not associated with headache or giddiness. He was discharged from hospital on September 29, with the diagnosis of a lesion in the region of the fourth ventricle. On October 1, he came to hospital for the first injection of a course of novarsenobillon. He was well the next day, but on the night of October 3, he had a fit in his sleep and died immediately afterwards.

A report of the post-mortem examination performed for the inquest, stated that the convolutions were flattened, and that there was definite hydrocephalus. The arachnoid was thickened over the lower aspect of the cerebellum, and the fourth ventricle was dilated. No other abnormality was detected. The vessels were all healthy, and there was no naked-eye evidence of syphilis.

Through the kindness of the late Dr. Brontë, and of the Resident Medical Officer who attended the inquest, pieces of brain-stem and cerebellum were brought back to the Hospital for further examination. There were several areas of petechial hæmorrhage in the substance of the cerebellum which resembled bruising. No definite meningeal thickening was visible.

Microscopically, however, all the septa of the cerebellum showed considerable fibrous thickening of the arachnoid with numerous miliary gummata, both in relation to the small meningeal vessels (fig. 1), and also in many places in the cortex and subcortical white matter of the cerebellum. Some were surrounded by zones of small round cells, chiefly lymphocytes; others were free from infiltration. The gummata were composed of elongated endothelial cells, usually arranged in whorls round a small vessel. Giant cells with many nuclei, not necessarily peripherally placed, were seen in several of the larger gummata, and in the centre of others was a core of degenerated tissue. Occasionally, giant cells and degenerated tissue were present in the same gumma. In the areas of ecchymosis the chief change was a great dilatation of small vessels with perivascular infiltration by small lymphocytes. In the pons an occasional vessel was ringed with lymphocytes, but no miliary gummata were observed. As far as could be ascertained from the limited material at our disposal, the ependyma covering the floor of the fourth ventricle was in most

places free from exudate or neuroglial tufts, but in the lateral angles of the ventricle a few sub-ependymal granulations were visible.

Summary of Case 3.

A man, aged 36, who admitted syphilitic infection, had the symptoms and signs of tabes dorsalis along with secondary optic atrophy, intense headache and vomiting. The latter symptoms were diagnosed as due to internal hydrocephalus. He died suddenly at home. The diagnosis was confirmed pathologically. There was intense gummatous meningitis and neuroglial proliferation in the floor of the fourth ventricle.

Case 3.—G. B., a married man, aged 36, was admitted to Hospital on June 30, 1926, under the care of Dr. Gordon Holmes. He had complained of headache for twenty-one months, of abdominal pain for three weeks, and of vomiting for a fortnight. The headache was localized to the back of the head and was worse at night. Vision had been poor in the right eye "for years," and was failing in the left. Difficulty in micturition had been noticed for five days previous to admission. He had acquired syphilis eight years before and had undergone a short course of treatment for this.

On examination, both optic discs were pale, the right more so than the left. The right pupil was larger than the left; both reacted to light and on convergence, but the left more sluggishly than the right. Muscular tone was diminished in the limbs. The knee and ankle jerks were absent and the plantar responses were flexor. The patient was an untrustworthy witness, but there seemed to be hypalgesia to pin-prick over the chest, the inner border of the arms, the outer side of the right leg and the inner side of the left leg. His gait was unsteady. No abnormalities were detected in the cardiac or respiratory systems.

Cerebrospinal fluid report: Whitish coagulum; cells 160 per cubic millimetre, 8 per cent. polymorphonuclears; total protein 0·05 per cent.; Nonne Apelt and Pandy positive; Lange, no change; Wassermann reaction positive, 4444 in cerebrospinal fluid and blood.

He was discharged from hospital on September 10, 1926, after a course of mercury and iodide, and was readmitted one month later on account of severe headache. He then had rigidity of the neck, pains in the arms and much vomiting. The right pupil did not now react to light. Cerebrospinal fluid report: Cells 12 per cubic millimetre; total protein 0·04 per cent.; Nonne Apelt and Pandy weakly positive; Lange 0112121000; Wassermann reaction positive 4321. A further course of mercury and iodide was given and he was discharged much improved on December 4, 1926.

On August 4, 1927, he was readmitted with a history of intense headache for nine weeks and vomiting of blood for a fortnight. Both optic discs now showed a post-papillitic atrophy. The left pupil was now larger than the right; both reacted to light through a small range, but better on convergence. The other signs remained the same. Cerebrospinal fluid report: Cells 60 per

cubic millimetre, 5 per cent. large mononuclears; total protein 0·035 per cent.; Nonne Apelt and Pandy very weakly positive; Lange 0011211000; Wassermann reaction positive 4444 in fluid and blood.

He was discharged from hospital on September 13, 1927, with the diagnosis of tabes dorsalis with internal hydrocephalus. He died suddenly at home on November 2, 1929. A post-mortem examination performed on November 5 by Sir Bernard Spilsbury was attended by one of us (J. G. G.). There were no external signs of disease. The brain and spinal cord were removed. A gummatous fibro-gelatinous meningitis was present over the base of the brain and the posterior surface of the cord, especially in the mid-thoracic region. On the ventral surface of the pons it covered the basilar artery so that this could barely be seen. There was in addition considerable internal hydrocephalus affecting all the ventricles. No softening of the hemispheres or evidence of hæmorrhage could be seen. The arteries at the base of the brain were fairly healthy. The viscera all appeared healthy.

Histologically there was a diffuse syphilitic meningitis over the pons, medulla and spinal cord. Over the ventral surface of the medulla it formed a fairly dense layer of fibrous tissue. The superficial layer of neuroglia was here considerably proliferated and in places had burst through the pial covering to blend with the newly formed connective tissue. The blood-vessels in this region were thick-walled and dilated. There was a considerable degree of ependymitis, the floor in the lower part of the fourth ventricle being covered by neuroglial tissue which filled the calamus scriptorius and spread as an even layer for some distance on either side of it. The walls of several vessels underlying the floor of the ventricle were heavily infiltrated with small cells. There was also considerable infiltration and thickening of the spinal meninges, most intense over the cervical region. The vessels in the spinal cord itself were very thick-walled and widely dilated, but showed no perivascular infiltration. In the mid-dorsal region there was a small inflammatory focus in the anterior horn composed of a mass of small round cells bearing no relation to blood-vessels. There was a slight degeneration of the posterior columns of the cord, most evident in the middle root zone of the lumbar enlargement and only appearing in sections of the thoracic and cervical cord as a diffuse pallor.

The fibres of the optic nerve were almost entirely replaced by neuroglia and fibrous tissue.

Summary of Case 4.

A woman, aged 30, had symptoms of increased intracranial pressure and signs which suggested a subtentorial lesion. Minor and major seizures occurred in hospital. On ventriculography the left ventricle contained more air than the right. No positive evidence of syphilis was obtained by an examination of the ventricular fluid and syphilis was not suspected from the history. The patient died following a subtentorial decompression. Pathologically the condition was one of obstructive

hydrocephalus, the fourth ventricle being lined by syphilitic granulation tissue which contained many miliary gummata and obstructed the foramina of Magendie and Luschka.

Case 4.—E. A., a married woman, aged 30, was admitted to hospital on February 10, 1930, under the care of Dr. Adie. For eighteen months there had been attacks in which the right hand "went dead" and in which she was momentarily unable to speak clearly. For seven months she had suffered from severe headaches, giddiness, vomiting and limpness of the arms. Latterly attacks of delirium had occurred during and after which she had been unable to see. Her health had otherwise been good except for "rheumatism" and there was nothing in the history to suggest previous syphilitic infection.

On examination she was found to be completely blind. The optic discs showed intense papillœdema with enormous retinal hæmorrhages. The right pupil was displaced upwards and inwards; it was small and very irregular in outline. The left pupil was larger, regular and circular. Both were inactive to light. There was complete paresis of the sixth nerve on the right side. The arms were hypotonic, inco-ordinate and tremulous on voluntary movement. The left knee-jerk was present, the right absent. The ankle-jerks were present and equal. Both plantar responses were extensor. The patient was doubly incontinent. Soon after admission she had a fit with loss of consciousness, and frequent attacks also occurred in which consciousness was not completely lost and from which it was possible to rouse her.

On February 27 a ventriculography was carried out which showed that the left ventricle contained more air than the right. The report on a specimen of ventricular fluid withdrawn at ventriculography was as follows: Cells 2·5 per cubic millimetres; total protein 0·02 per cent.; Nonne Apelt and Pandy negative; glucose 0·069 per cent.; Lange, no change; Wassermann reaction doubtful.

A subtentorial decompression was performed on March 4. The patient did not rally after the operation and died the same day. A limited post-mortem examination was carried out four hours after death, the brain only being removed. No tumour was found, but there was considerable hydrocephalus of all the ventricles, including the fourth. The meninges over the front of the pons and over the foramina of Luschka were considerably thickened. The foramen of Magendie was extremely small. The floor and roof of the fourth ventricle were granular. There was a greyish diffuse thickening of the pia arachnoid over both frontal lobes; the cortex here was thin and firm, and the pia mater unduly adherent. On section granular ependymitis was especially obvious in the fourth ventricle where the calamus scriptorius was filled up with exudate, but was also present in the lateral ventricles.

Histologically the whole surface of the fourth ventricle was covered by a layer of newly-formed tissue composed of fibroblastic and endothelial cells and containing a few giant cells and a number of lymphocytes. This overlay the ependymal layer which was broken in many places by tufts of neuroglia which projected into, and fused with, the new membrane. Immediately under the

ependymal layer the vessels were all intensely infiltrated and small gummata could be seen forming round many of these by proliferation of fibroblastic and endothelial cells: deeper in the tissues there was practically no perivascular infiltration or other alteration in structure. This condition extended as high as the iter of Sylvius but not into the lateral ventricles. In some places small gummatous nodules were formed in the new membrane and in many places giant cells lay free, or loosely attached, on the ventricular surface. A membrane of similar character filled the basilar cistern and covered the ventral surface of the upper medulla. It contained numerous miliary gummata with giant cells, and giant cells were also seen lying more diffusely in the superficial layers of the membrane (figs. 2 and 3). Some of them appeared to be almost free in the subarachnoid space. The pia mater in this region was broken through in several places by tufts containing a feltwork of fully differentiated neuroglial fibres which passed in between the gummata or merged with the overlying exudate. The roots of the seventh, eighth and ninth nerves as they passed out from the cerebellar-pontine angle were embedded in the exudate and a few giant-celled miliary gummata lay among the nerve-fibres. At a rather higher level, over the ventro-lateral surface of the pons, was a larger gumma, measuring 1·5 mm. transversely and rather less than 1 mm. in thickness. It was largely structureless but was penetrated by thin strands of collagen.

Summary of Case 5.

A woman, aged 35, who had always been subnormal mentally and who had suffered from fits as a child, had symptoms of increased intracranial pressure and the signs of a left subtentorial lesion. Her mother had been under treatment for neurosyphilis for five years, and all except one of her five brothers and sisters had had fits as children. The patient died after a subtentorial decompression. At the autopsy, hydrocephalus of all the ventricles and a peculiar degeneration of the choroid plexus were found.

Case 5.—D. H., a single woman, aged 35, was admitted to hospital on July 27, 1930, under the care of Dr. Gordon Holmes. She had been completely blind for five weeks. She had complained of pain in the back of the head and neck for seven months, and of unsteadiness in walking with failure of vision for three and a half months. Amenorrhœa had been present for six months. She had always been mentally very backward and had had fits from birth until the age of 14, when they ceased with the onset of menstruation. The headache which dated from January, 1930, started in the back of the head and radiated forwards towards the eyes; it was worse on rising in the morning. In February, 1930, she had a fit lasting for thirty minutes during which she was unconscious but not convulsed. Subsequently the headache became more intense and generalized and was frequently accompanied by vomiting. The sight failed rapidly from March, 1930. Five weeks before admission she was noticed to have a rolling gait.

Family history.—Her father died of appendicitis at the age of 43. Her mother, aged 64, had been psychotic for about twelve years with visual hallucinations and delusions of grandeur. For the past five years she had been attending the Maida Vale Hospital for Epilepsy and Paralysis for courses of novarsenobillon. Of the four sisters of the patient, the two older, and one younger, had had fits as children, whilst her brother had had fits at the age of about 20, but was now apparently healthy and had two healthy children.

On examination the patient was found to be of inferior mentality. She was co-operative but not attentive. She perceived odours but could not distinguish essential oils from asafœtida. She had no perception of light. The optic discs were of a grey colour; there were a few small hæmorrhages in the right disc and about 2 dioptres of swelling; the left disc was swollen to 3 dioptres. The ophthalmological report (Mr. Paton) stated that there was more vascular change in the retina than was usual in cerebral neoplasms and suggested a syphilitic origin for the condition. The pupils were irregular and gave a slight unsustained reaction to light but no reaction on attempted convergence. A moderately fine, rapid nystagmus with the quick component to the left occurred on looking to the left, and a coarser, rotatory nystagmus on looking to the right. There was some impairment of upward conjugate movement, but no apparent paresis of the external ocular muscles. The right corneal reflex was more sluggish than the left. The jaw deviated to the right and the left masseter muscle contracted better than the right. There was no movement of the palate and the pharyngeal reflexes were absent. The right trapezius muscle was weak and the tongue deviated to the right.

Both flexion and hyperextension of the neck caused pain. Tone was diminished in the left arm and leg. There was some inco-ordination on both sides but more on the left than on the right. Perception of pain was generally impaired. The left arm reflexes were brisker than the right. The abdominal reflexes were sluggish, but better on the right side, while the knee and ankle jerks were brisker on the left side; the left plantar response was extensor, the right flexor. The apex beat of the heart was loud and sharp and preceded by a pre-systolic murmur. The Wassermann reaction in the blood was negative. A subtentorial decompression was performed on August 13. The patient died next day.

A post-mortem examination was made about twenty-four hours after death, the brain only being removed. There was considerable hydrocephalus of the lateral and third ventricles. The meninges over the base of the brain were considerably thicker than normal. On section a gelatinous exudate was seen on the floor of the fourth ventricle, so that the usual glossy appearance was lost. The calamus scriptorius also seemed to be filled up with this material. A slight degree of granular ependymitis was present in the lateral ventricles.

There was a localized swelling of each choroid plexus at the junction of the lateral and inferior horns of the lateral ventricles which was firm and yellowish in colour, and measured 1½ cm. in diameter. Histologically they were composed of knots of varying size which consisted chiefly of laminated crystals of

cholesterin with a varying admixture of calcium salts surrounded by several layers of fairly thin connective tissue. Irritation giant cells were very abundant around the cholesterin plaques, passing in some distance between them. There was some small-celled infiltration around the vessels between these knots. Numerous corpora amylacea were present amongst the connective tissue of the plexus.

On microscopical examination the meninges over the pons and medulla were found to be thickened, but nowhere was there any evidence of either diffuse or perivascular cellular infiltration. The walls of many of the blood-vessels in the meninges over the base of the brain were thickened and appeared to be undergoing hyaline degeneration. There was no sub-pial overgrowth of neuroglia and the ependyma covering the floor of the fourth ventricle was fairly normal, but at the lower end of the calamus scriptorius it was covered in places by outgrowths of neuroglia. There was also slight granular ependymitis on the walls of the lateral ventricles. The blood-vessels in the neighbourhood of the ventricles were thickened but not infiltrated.

Summary of Case 6.

A woman, aged 45, had symptoms of increased intracranial pressure. The cerebrospinal fluid afforded positive evidence of neurosyphilis, and after a course of treatment the symptoms were relieved. While in hospital she suddenly became drowsy, then comatose, and died suddenly after a convulsion. The foramina of the fourth ventricle were almost obliterated by arachnoidal adhesions, which caused obstructive hydrocephalus.

Case 6.—E. D., a married woman, aged 45, was admitted to Hospital, under the care of Dr. Gordon Holmes, on April 4, 1931. She complained of dragging of the left leg, pain in the back and unsteadiness in walking. All these symptoms had been present for about one month. For about five months she had had attacks of severe headache, localized to the back of the head, always worse in the morning, and occasionally accompanied by vomiting. The headache had recently become much more severe and the vomiting frequent and copious. For two weeks the vision had been failing, and, following an attack of double vision a few days previously, almost complete blindness supervened four days before admission to hospital.

Previous history.—In January, 1929, radium had been inserted into the cervix uteri for carcinoma.

On examination, she was extremely dull and uncooperative. She could read letters of one inch at a distance of two feet. The margins of the optic discs were blurred and there were about 2 dioptres of swelling in each. The retinal arteries were small and the veins engorged. The right pupil was larger than the left; both reacted to light, but the contraction was not maintained, and they reacted slightly on convergence. There was right-sided ptosis. No conjugate upward movement of the eyes was possible, and conjugate movement

to the left was weak. Nystagmus was present on looking to either side. The right side of the face was weak; the palate was drawn to the right, and the pharyngeal reflexes were absent. There was a rhythmical tremor of the outstretched hands. Both knee and ankle jerks were exaggerated. The right plantar response was flexor, the left extensor. The sense of position was lost in the left hand and impaired in the right. Joint sense was grossly defective in the hands and feet. Pain was everywhere well appreciated. She showed signs of meningeal irritability and stiffness of the neck. No abnormalities were detected in the cardiovascular or respiratory systems. Cerebrospinal fluid (April 8): Cells, 54 per cubic millimetre; 7 per cent. large mononuclears, 3 per cent. polymorphonuclears; total protein, 0·055 per cent.; Nonne Apelt weakly positive, Pandy positive; Lange, 4545533332; Wassermann reaction positive, 4442 in fluid, 4442 in blood.

After a course of six injections of novarsenobillon, her headaches became less severe, and the range of ocular movement less limited. A second report on the cerebrospinal fluid on May 26 was as follows: Cells, 47 per cubic millimetre, with 8 per cent. large mononuclears; total protein, 0·045 per cent.; Nonne Apelt negative, Pandy weakly positive; Lange, 4443432100; Wassermann reaction positive, 4420 in fluid, 4310 in blood.

On June 4, she suddenly became drowsy and quickly stuporose, and developed a right hemiplegia. She died later in the evening of respiratory failure after a sudden convulsion.

A post-mortem examination was made less than twelve hours after death. The skull was thin. The dura mater was tense over the vertex, and fenestrated over the frontal poles where the inner surface of the frontal bone was roughened and eroded in places. Over the middle cranial fossa the dura mater was thinned with small fenestrations through which the cerebral cortex was herniated. The arachnoid over the base of the brain was thick and tough, but its reticulum was not filled up or infiltrated. The cerebellar tonsils were glued to the dorsal surface of the medulla by firm arachnoidal adhesions so that there did not appear to be a cisterna magna. Over the left foramen of Luschka the arachnoid was ballooned out: over the right there were adhesions which seemed to obliterate it. There was no thickening of the arachnoid over the vertex of the brain. The ventricles were all greatly distended. Fine granulations were present in the lateral ventricles, but were not so obvious in the floor of the fourth ventricle. In the cervical region of the spinal cord the dura was adherent to the arachnoid. Elsewhere the arachnoid was thickened, and of a milky colour on both surfaces of the cord. Both middle cerebral arteries in the fissure of Sylvius were white, but had a lumen. The other arteries at the base of the brain were rather dilated, but not atheromatous. The lungs were healthy. The pericardium was adherent to the heart, which was enlarged, with thin, flabby, fatty walls. The valves appeared healthy. There was some atheroma round the origins of the coronary vessels, and very fine, streaky atheroma above the aortic cusps. The liver appeared healthy macroscopically, but microscopically was found to contain numerous miliary gummata. In the

aorta the vasa vasorum were thickened, but there was no perivascular infiltration and no infiltration of the media.

In the basal ganglia there were two triangular areas of intense gliosis, one in the innermost part of the globus pallidus, and the other just under the claustrum. In these areas there were many rod cells and enormous numbers of fibrous astrocytes with fairly thick processes. The blood-vessels in the vicinity were heavily infiltrated with small lymphocytes. The myelinated fibres passing through these areas of gliosis appeared normal; but that some destruction of myelin had taken place, was indicated by lipoid round the vessels, and the presence of numerous fat granule cells in sections stained by Scharlach R.

The cerebral meninges were diffusely thickened and infiltrated in the sulci. The vessels running into the medulla were hyaline, their walls were infiltrated, and they were surrounded by many corpora amylacea. There was considerable proliferation of the subependymal neuroglia in the lateral and fourth ventricles. The ependyma in the lower part of the fourth ventricle was covered by a new layer consisting chiefly of neuroglia, but in some places also containing collagen fibres. Hyaline changes were found in the walls of the vessels under the floor of the fourth ventricle, and the choroid plexus in this situation contained many calcified nodules. The spinal meninges were thickened, and an occasional fibrous knot, ringed with lymphocytes, was present over the cervical region of the cord. In Weigert Pal preparations of this level the column of Goll was pale, and in sections stained by Mallory's method a neuroglial overgrowth was visible. In the eighth cervical and first dorsal segments, the anterior horn cells were rounded, shrunken and vacuolated.

Summary of Case 7.

A man, aged 44, who admitted venereal infection, gave a history of fits and difficulty in walking. His signs were those of a tetraplegia accompanied by multiple cranial nerve palsies. He died of hypostatic pneumonia and pathologically there was hydrocephalus due to obstruction of the foramina in the fourth ventricle by syphilitic granulation tissue containing miliary gummata. A large meningeal gumma was present over the upper cervical region of the cord.

Case 7.—E. H., a married man, aged 44, was admitted to Hospital on October 6, 1922, under the care of Dr. Aldren Turner. In 1903 he had acquired venereal disease and had been treated for a few weeks. In 1917 he had two attacks of unconsciousness, each lasting two minutes, and since then had complained of difficulty in walking, pains at the back of the neck, a sensation of "pins and needles" in the hands and attacks of trembling and giddiness. Recently bladder control had been lost.

Examination: The patient was a well-nourished man. His memory, though good, had deteriorated. His speech was normal: his smell was defective. His vision was $\frac{6}{18}$ in the right eye, $\frac{6}{36}$ in the left. The optic

discs were pale and the right was a little blurred. The pupils were equal, central and regular: they reacted to light but quickly dilated, and reacted to accommodation. Lateral deviation of the eyes to the left was difficult and on extreme lateral deviation there were coarse irregular nystagmoid jerks. The left eye seemed more prominent, and there was less retraction of the left eyelid than of the right. The right masseter and temporal muscles were weak. Both corneal reflexes were brisk. There was slight weakness of the left orbicularis oculi. The tongue was protruded to the right; it showed a slight tremor, but no atrophy. The right grasp was stronger than the left. Co-ordination was poor in all limbs. Sensation to pain and light touch was unimpaired, but muscle sense, vibration and the sense of position were lost in the arms and legs. The deep reflexes were brisk and equal. The plantar responses were flexor. The gait was ataxic and the toes of the right foot were dragged along the ground. The cardiovascular and respiratory systems appeared healthy.

Cerebrospinal fluid: Cells 33 per cubic millimetre, consisting of large and small mononuclear cells and about 15 per cent. of polymorphonuclear: total protein 0·05 per cent. Nonne Apelt positive: Lange 0223422110: Wassermann reaction positive, 4444 in cerebrospinal fluid, 4320 in blood.

During the last week in December, 1922, sudden weakness of the right arm and leg developed, followed a week later by weakness of the left arm and leg. On January 8, 1923, the pupils were irregular, the left larger than the right; they still reacted to light. There had been occasional diplopia. On lateral deviation of the eyes there was now well-marked nystagmus, rapid on looking to the right, slow on looking to the left. The area supplied by the left fifth nerve, and by the second and third divisions on the right side, were analgesic. The right side of the face was weak and the sense of taste was lost. The patient was deaf in both ears and had vertigo, objects rotating to the right side. There had been occasional dysphagia, but the palate moved well. Both arms were spastic and were flexed across the chest. The right arm and leg were completely powerless. All movements of the left arm and leg were possible but weak. A to-and-fro tremor was present occasionally in the right arm, and involuntary jerking of the right arm and leg caused the patient much annoyance. Even more troublesome was a jerking of the left leg, which occurred only at night and which was followed by pain. A persistent dull pain radiated from the seventh cervical spine to the front of the chest, and there was some hyperæsthesia over this area. The sense of pain and light touch was almost completely lost over the whole of the left side of the body below the clavicle. All the reflexes were exaggerated and both plantar responses were now extensor. During the remainder of January the patient became weaker and signs of hypostatic pneumonia appeared in the lungs. His neurological signs remained unchanged till he died on January 31.

A post-mortem examination was made twenty-four hours after death. The brain and spinal cord were removed together with the left retina and optic nerve and the contents of the right orbit. At the base of the brain and over

the cervical region of the cord the dura mater was extremely adherent to the pia arachnoid. No cisterna magna could be made out, all the membranes being matted together. The medulla was softened, greyish in colour, and flattened by distension of the fourth ventricle. There was much hydrocephalus. Except at the base of the brain and over the cervical region of the cord, there was no adhesion between the arachnoid and the dura, and the dura was nowhere thickened. The spinal cord was pale, swollen and softened in the cervical region. A few small gummata were present on the posterior surface of the cord, one at the origin of the roots of the cauda equina being especially large. The upper cervical cord was grossly distorted through compression by a gumma in the meninges on the postero-lateral aspect of the cord, measuring 9 mm. in transverse diameter and 5 mm. in thickness. Its outer part was firm and fibrous; its central part, caseous and necrotic. The meninges in this region were enormously thickened, measuring about 3 mm. in diameter.

Histologically there was fairly severe infiltration of the cortical meninges, especially in the depths of the sulci, but the cortical vessels although thickened were not infiltrated. Granular ependymitis was seen in the lateral ventricles and there was slight infiltration of many of the small sub-ependymal vessels. In the mid-brain and pons all the vessels were dilated and thickened, and those under the ventricular surface were surrounded by wide cuffs of lymphocytes. In the iter and on the floor of the fourth ventricle the ependyma was covered by a thick layer composed partly of neuroglial elements in which fibrils could be demonstrated, but mainly of a cellular connective tissue. There was considerable proliferation of the sub-ependymal neuroglia in this region and in many places the line of ependymal cells was broken. The calamus scriptorius was filled up by a mass consisting partly of neuroglia which had overgrown the ependyma, and partly of the choroid plexus which was infiltrated with small cells and contained several miliary gummata. Dense perivascular infiltration and a few miliary gummata were also seen under the floor of the ventricle in this region.

The pia-arachnoid was infiltrated and thickened over the pons and medulla. On the dorso-lateral surface of the medulla at its lowest level there was a remarkable outgrowth of neuroglia into the meninges, so that a superficial zone was formed in which areas of neuroglia were intersected and penetrated by collagen fibres (fig. 4). There was also in this region, especially near the median raphe, considerable overgrowth of connective tissue round the walls of the vessels, the new fibres being chiefly arranged parallel to the vessel walls, but short radial projections also extended from them into the nervous tissue.

In addition to the large gumma in the meninges of the upper cervical cord, several smaller gummata were also seen in this region and large masses of lymphocytes were scattered throughout the meninges in all regions of the cord. Many of these were localized round blood-vessels and probably represented an early stage in gumma formation. The vessels in the cord were

thickened and widely dilated, but no perivascular infiltration was seen inside the cord. In the upper cervical region where the cord was compressed and distorted it was difficult to identify the various fibre tracts by the Weigert Pal method, but as far as could be ascertained the chief loss of myelin was around the periphery of the cord, an appearance to which the name of "syphilitic halo" has been given. This appearance was even more evident in lower segments of the cord where the pallor at the periphery contrasted strongly with the well myelinated fibres in the central zones (figs. 6 and 7). The nerve-roots throughout the cord, even in that portion which was compressed by the gumma, were well myelinated.

The retina and left optic nerve appeared normal except for slight œdematous changes at the nerve head.

Discussion.

It has already been noted that Oppenheim, under the heading of "Diffuse Gummatous Meningitis," described a clinical picture which resembles closely that presented by our cases. The salient points in this syndrome are early headache, later vomiting and vertigo, with attacks of loss of consciousness or general convulsions, a moderate degree of dementia with failure of memory and apathy, attacks of stupor lasting for several hours or days and separated by long intervals of full consciousness, paralysis of various cranial nerves, especially those of the eye, and commonly papillœdema and consecutive optic atrophy. He considered that these symptoms were caused by widespread basal meningitis. But loss of consciousness, attacks of stupor and reduction of intelligence suggest a more general affection of the brain, of which the most probable cause is increase of intracranial pressure. Headache and papillœdema are probably also caused by hydrocephalus, although they might possibly be due to more local conditions. On the other hand basal meningitis is certainly the cause of the cranial nerve palsies which are so constantly present, and which, by their protean nature, distinguish syphilitic hydrocephalus from other forms of intracranial hypertension.

Headache was present in all our cases and was usually the first symptom. In one case it preceded all other symptoms by four years; in the others it was associated soon after its onset with other symptoms, of which the most common were diplopia and attacks of various kinds. It was often severe and resembled the headache of cerebral tumour in being accompanied by vomiting, giddiness, or difficulty in walking. Most commonly the headache was localized in the back of the head and the neck. That it was due to intracranial hypertension was indicated,

in some cases, by the early presence of papillœdema and consecutive optic atrophy.

Attacks of loss of consciousness, sometimes convulsive in character, occurred during the course of the illness in four cases, and terminal convulsions were present certainly in one, and probably in two of the others. In Cases 1 and 2 some of the attacks were of an unusual character. In Case 1 there were purely tonic fits, with temporary loss of consciousness, in which the arms were adducted and extended across the front of the trunk. These attacks may have had some relation to tetany, of which also the patient had two attacks. In Case 2 seizures occurred which were typical instances of the "vaso-vagal attacks" described by Gowers. In these the patient felt cold all over, broke out into a cold sweat, and for about ten minutes, although perfectly conscious, was unable to move a muscle or to open his mouth to speak. Gowers attributed attacks of this kind to an affection of the medulla, and, although we were unable to confirm this owing to the limited pathological material at our disposal, it is significant that in this case the meningitis round the foramen of Magendie was more intense and acute than in any of the others. In only one of our cases (Case 5) were there attacks of complete loss of consciousness without convulsions, but in Case 4 there were somewhat similar attacks in which consciousness was not completely lost, so that the patient could be roused. In no case were there prolonged attacks of stupor such as Oppenheim describes, but in Case 6 there was extreme mental dullness throughout the three months that the patient was in hospital.

Cranial nerve palsies were prominent in every case and instances of paralysis of each individual cranial nerve were encountered. Oculomotor palsies were the most common, occurring in all except Case 2. In Cases 1, 2 and 6, diplopia was one of the early symptoms. Defective upward movement of the eyes was noted in three cases and ptosis, inequality of the pupils, strabismus and nystagmus were also seen. These oculomotor palsies were often combined with weakness of the jaw, face, palate, pharynx or tongue, usually greater on one side. This association indicated a widespread affection of the basal meninges which was actually found at the post-mortem examination.

Papillœdema was present in all except Case 2, and in four cases had progressed to optic atrophy. In two cases blindness had set in rapidly becoming complete in one of these within two weeks after diminution of vision was first noticed. In Case 5, in which the syphilitic infection was probably congenital, there were, in addition to "secondary"

atrophy, vascular changes in the retina of a syphilitic nature. While it is unsafe to suppose that every syphilitic patient who has papillœdema is suffering from hydrocephalus, it seems probable that in this series of cases the papillœdema and optic atrophy were due rather to the general increase of intracranial pressure than to meningeal inflammation around the optic nerves. In the only case (Case 3) in which there was gradually progressive optic atrophy, the patient had severe headaches between his periods of hospital treatment, and the appearance of his optic discs was that of post-papillitic rather than of "primary" optic atrophy. It is possible that in his case the local sclerosis of tabetic atrophy combined with the increase of intracranial pressure to destroy the optic nerve.

Weakness or sensory disturbances in the trunk and limbs were not prominent in our cases, although in one case there was a severe tetraplegia due to meningomyelitis of the cervical cord. In three a slight degree of hemiplegia was present, and it is noteworthy that in none of these did the distribution of paralysis in the cranial nerves suggest a cortical or capsular lesion; and, in effect, no lesion above the brain-stem was found in them. The only foci of cerebral softening found in our cases were two minute areas in the lenticular nucleus in Case 6, and these apparently had not given rise to any symptoms.

The unsteadiness of gait, and inco-ordination, limpness and weakness of the arms from which several of the patients suffered are not easily explained on a pathological basis. To some extent they may have been due to the hydrocephalus, but in several cases the presence of vertigo, nystagmus or gross ataxy of the arms suggested a lesion of the vestibulo-cerebellar system. Except in Case 2 there was no pathological evidence of damage to the cerebellum or the deeper tracts of the brain-stem, although the most superficial fibres undoubtedly suffered in some cases; on the other hand, there was considerable cellular infiltration, and sometimes gummatous formation, in the sheaths of the eighth nerves. It seems therefore possible that these symptoms were due, at least in some cases, to injury of the vestibular nerve; in Case 1 this was rendered still more likely by the association of tinnitus with the attacks of giddiness.

Pathological Anatomy.

The most important question that arises in a survey of the pathology of these cases is the mechanism of the hydrocephalus. To gain an exact knowledge of this under the conditions of an ordinary post-mortem

examination may be difficult or even impossible when the hydrocephalus is of the communicating type. Penfield and Elvidge have suggested injecting a suspension of indian ink under pressure into the ventricles, as soon after death as possible, and determining the position of the block in the subarachnoid space at the subsequent post-mortem examination by the staining of the meninges. Unfortunately, we did not know of this technique at the time of autopsy nor was hydrocephalus suspected in any of the cases in which the autopsy was performed at the National Hospital. While the presence of arachnoidal thickening round the pons and in the cisterna basalis suggests an obstruction to the passage of cerebrospinal fluid from the posterior to the middle cranial fossa, it is impossible to determine the degree of obstruction after the brain has been removed from the skull. Even Penfield and Elvidge's method gives little indication of the defect in the absorption of cerebrospinal fluid, although from Dandy's classical experiments it may be assumed that hydrocephalus will result whenever the passage of fluid from the posterior to the middle cranial fossa is completely blocked. Even an incomplete block in this situation would probably produce some degree of hydrocephalus, and certain of the milder syphilitic cases which yield to medicinal treatment are no doubt caused in this manner.

Narrowing of the foramina of Magendie and Luschka is a more obvious cause for hydrocephalus, and its effect in obstructing the passage of fluid is easier to assess. But after the brain has been hardened in formalin it is almost impossible to ascertain the condition of these foramina. We were able to make a careful examination of the foramina at the autopsy in four of our cases, but in Case 2, an inquest case, and in Case 5, in which the autopsy was performed during a holiday period, no such examination was made. In Case 3, there was no obvious blockage of the foramina; as this patient had benefited considerably from three periods of hospital treatment which included lumbar puncture, it seems likely that here the hydrocephalus was of the communicating type.

In the other four cases (1, 4, 6 and 7) there was very definite evidence of blockage of the foramina of exit from the fourth ventricle. The usual condition in these cases was that the cerebellar tonsils were glued down over the back of the medulla obstructing the foramen of Magendie, and that the foramina of Luschka were obliterated by meningeal thickening, the fourth ventricle was ballooned out and the cisterna magna was empty. It is probable that the closure of the foramen of Magendie was caused to some extent by the intense granular

ependymitis, which had filled up the calamus scriptorius with newly formed tissue.

It is unfortunate that no special examinations were made during life in any of our cases to determine the freedom of communication between the ventricles and the lumbar theca. From the point of view of treatment this knowledge is of the greatest value, as it is improbable that cases of non-communicating hydrocephalus can be saved by lumbar puncture and anti-syphilitic treatment alone. Even in Case 3, which was probably of the communicating type, this treatment did not prevent progressive blindness and eventual death. In Cases 1, 4 and 5, lumbar puncture was not performed and the true nature of the condition was not diagnosed. In two of these (Cases 1 and 4) the Wassermann reaction was negative in the blood although in Case 1 there were gummata, both of the giant-celled and necrotic types, in the meninges. In Case 4, where the infection was probably congenital, no progressive syphilitic lesions were present in the nervous system, and had it not been for the family history and the knowledge that the patient's mother was undergoing anti-syphilitic treatment the diagnosis would have been difficult even after a histological examination of the brain.

The *microscopical study* of these brains brought out two features in the histopathology of tertiary neurosyphilis which seem to be somewhat neglected in descriptions of the disease. These were (1) the intensity of the neuroglial reaction round the medulla both on its ependymal and pial surfaces, and (2) the frequency with which giant-cells were present in the syphilitic granulation tissue.

(1) *Granular ependymitis* is well known to occur in general paralysis as small discrete projections of neuroglia through the ependymal lining of the ventricles. In most of our cases however, the ependymitis was much more intense, so that a gelatinous mass filled up the calamus scriptorius and was spread in a thin layer over the lower part of the ventricle, completely covering the ependyma. The frequency with which the subependymal vessels were heavily infiltrated with lymphocytes indicated the inflammatory nature of this new membrane. In Cases 4 and 7 this was very evident. Here the new membrane was composed not so much of neuroglia as of fibroblastic and endothelial cells with, in Case 4, numerous giant-cells and minute gummata; in the latter case it completely covered the walls of the fourth ventricle up to the iter of Sylvius. The condition resembled fairly closely that which may be seen in tuberculous meningitis, except that it was of more chronic nature with a considerable overgrowth of neuroglial fibres in the

deeper layers of the membrane. It was quite evident in these cases that inflammation from the basal meninges had spread into the fourth ventricle and permeated it from below upwards; and it is probable that the pathogenesis of the neuroglial overgrowth in the other cases was similar although in them the inflammation was less acute.

Less attention has been paid to the neuroglial outgrowths through the pia mater over the ventral surface of the medulla. These were described and figured by Purdon Martin in syphilitic amyotrophy, and by Lhermitte in tertiary neurosyphilis. They were seen in four of our cases, and are probably fairly common in gummatous basal meningitis. Like the ependymal granulations they appear to be of inflammatory origin, the proliferation of the subpial neuroglia being stimulated by chronic inflammation in the pia-arachnoid. Whether the rifts in the pia mater are primary or secondary is a difficult question to decide. It seems most probable that they are directly due to the inflammatory changes in this membrane, since the subpial neuroglia almost constantly proliferates in cases of syphilitic meningitis, but rarely bursts through the pia mater. Further evidence of the inflammatory nature of the neuroglial overgrowth is provided by the presence of cuffs of lymphocytes around the subpial vessels in the more acute cases.

The marginal pallor of the cord in Weigert-Pal sections, to which the name "syphilitic halo" has been given, is clearly of similar origin. For this we must postulate a progressive destruction of the myelinated fibres which lie nearest to the inflamed pia mater by toxins passing inwards from this membrane. This marginal degeneration is not uncommonly present in long-standing cases of syphilitic meningitis. It was well described and figured by Purdon Martin in syphilitic amyotrophy, and Léri also mentioned it as occurring in that condition. It was present in only two of our cases and therefore appears to be less often met with in the more acute and diffuse forms of syphilitic meningitis than in syphilitic amyotrophy, in which, in our experience, it is almost constantly present. It is noteworthy that these were the only two cases in which the gummata in the meninges were large enough to be visible to the naked eye. Even in these they were of small size, the largest, that on the cervical cord in Case 7, being only about one centimetre in diameter and half a centimetre in thickness.

(2) *Giant-celled gummata* of minute size were present in Cases 1, 2 and 4, and were the most striking feature of the inflammation in Cases 2 and 4. In Case 6 they were found in the liver only. Jakob has recently drawn attention to their common occurrence in syphilic meningitis, and

has demonstrated them also in the cerebral cortex. It is probable that the comparative rarity at the present time of the larger meningeal gummata, and the frequency with which these minute gummatous formations are found, may be correlated with the alterations in therapy which have taken place during the last twenty years. Treatment with arsenic and bismuth does not appear to have greatly influenced the incidence of neurosyphilis, but it does seem to have reduced the size of gummata in the nervous system and probably also throughout the body.

From a histological examination alone it is often difficult to distinguish the condition of the meninges and the floor of the fourth ventricle in a case such as E. A. (Case 4) from that seen in tuberculous meningitis. The most important distinction is that the nuclei of the syphilitic giant-cells are usually present throughout the cell body and are not, as in tuberculous giant-cells, confined to the periphery. Jakob lays considerable emphasis on this distinction. There is also a much greater tendency for collagen fibres to be present in a syphilitic gumma. Still more important is the discovery of the causative organisms in the nodule. While it is usually possible to see tubercle bacilli in giant-celled tubercle nodules, spirochætes are not often found in miliary gummata; we were unable, in spite of careful search, to find them in any of our cases. But the knowledge that the Wassermann reaction is positive in both blood and cerebrospinal fluid, as in Case 2, makes the diagnosis reasonably certain.

Conclusions.—(1) Hydrocephalus is a fairly common result of basal gummatous meningitis. Although it is usually of the communicating type, complete obstruction of the foramen of Magendie is not uncommon, and the foramina of Luschka may also be sealed up by plastic meningitis. (2) At the present time syphilitic hydrocephalus is a more common post-mortem finding than the larger syphilitic gummata of the meninges on which more emphasis was laid in the past. Minute gummata, sometimes of the miliary giant-celled type, are often present in hydrocephalic cases. (3) The ependymitis and extra-pial outgrowths of neuroglia associated with gummatous meningitis are direct results of inflammation in relation to these membranes. Degeneration of the myelinated fibres on the surface of the spinal cord also occurs in long-standing cases.

We desire to express our thanks to the medical staff of the National Hospital, Queen Square, for permission to use the clinical records of the Hospital, and especially to thank Dr. James Collier and Dr. Gordon Holmes for their helpful interest.

The pathological examination of these cases was aided by a part-time grant from the Medical Research Council.

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PLATE LEGENDS.

FIG. 1 (*Case* 2).—Section of cerebellar cortex. Several small giant-celled gummata are present in the pial septa, and minute early gummatous formations are seen along the lines of the small vessels in the molecular layer of the cortex. m = molecular layer; g = granular layer; p = pial septa.

FIG. 2 (*Case* 4).—Lateral surface of medulla. Four small gummata surrounded by darkly staining neuroglia fibres are present in the inferior medullary velum. The pial septum is heavily infiltrated with small cells. (Mallory's phosphotungstic acid hæmatoxylin stain.)

FIG. 3 (*Case* 4).—Ventricular wall of the fourth ventricle. Two giant cells lie free on the surface. A small gumma and a heavily infiltrated vessel are seen just under the line of the ependyma.

FIG. 4 (*Case* 7).—Dorso-lateral surface of medulla. The darkly staining fibres of the pia mater are seen irregularly penetrating the paler neuroglial outgrowths. The entering vessels near the dorso-mesial septum are thickened and infiltrated.

FIGS. 5 AND 6 (*Case* 7).—Sections of cervical and lumbar enlargement of cord showing peripheral zone of demyelination. The nerve-roots at the cervical level are darkly stained. (Weigert-Pal method.)

FIG. 1.

FIG. 2.

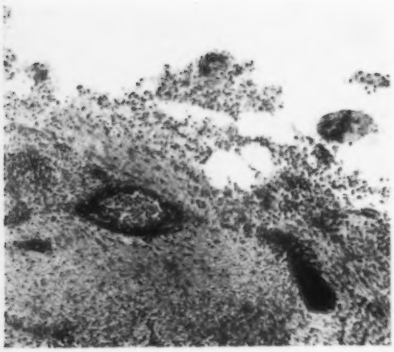

FIG. 3.

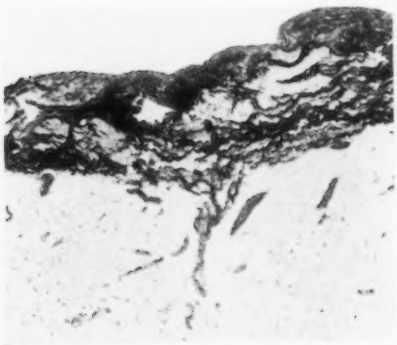

FIG. 4.

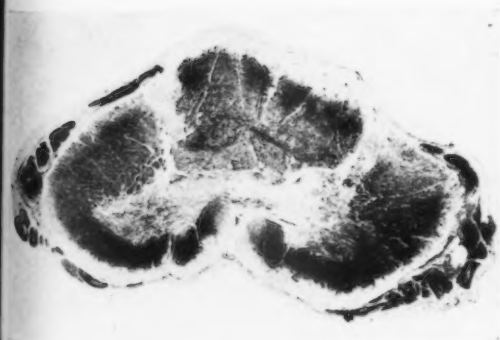

FIG. 5.

FIG. 6.

To illustrate paper by Greenfield and Stern.

ON THE PHARMACOLOGY OF THE GRASP REFLEX.

BY CURT P. RICHTER AND ARTHUR S. PATERSON.[1]

Psychobiological Laboratory, Henry Phipps Psychiatric Clinic, Johns Hopkins Hospital, Baltimore, Md.

KNOWLEDGE regarding the mechanisms involved in the grasp reflex is still very limited, all data available at present having been obtained from two sources: the normal newborn infant, and the adult with lesions of the frontal lobes of the brain or underlying structures. It is a well-known fact that the human infant shows this reflex for several months after birth, usually until voluntary grasping begins. After that, this phenomenon seems never to appear spontaneously again, except with destruction of the cerebral areas already mentioned. It has been demonstrated in previous papers, however, that a reflex grasping response can be induced in adult monkeys by hypodermic injection of bulbocapnine (Richter and Paterson, 1931), and by inhalation of carbon dioxide gas in high concentrations (Richter and Paterson, 1932). On the basis of these observations, it seems possible that the pharmacological aspects of the problem may prove very significant. From this point of view, the above experiments have been repeated with several other drugs to determine whether the reflex can be brought out by any agents besides bulbocapnine and carbon dioxide, and if so, by any special group of such agents.

METHODS.

All of the monkeys used in these experiments were of the *Macacus rhesus* species and had attained at least half their full growth. The technique for eliciting and measuring the reflex in adult animals, described in detail in previous papers, is based upon the fact stated above, that a normal monkey beyond infancy will not hang from a horizontal bar placed within its grasp (Richter, 1931). However, an adult animal in which the reflex has been elicited by some abnormal condition will grasp the rod and hang from it by one hand for an

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appreciable length of time. This time interval may be regarded as a measure of the strength of the reflex.

In order to simplify the procedure, both legs and one arm were tied and one hand left free for testing. The two hands were tested alternately at frequent intervals following the administration of the different drugs.

These were given in varying strengths, usually up to the minimum lethal dose, most of them by hypodermic injection, but some of them orally, intravenously, or intraperitoneally.

Results.

Sixteen of the twenty-three drugs used in these experiments produced a condition in which the grasp reflex could be elicited. These drugs, showing in common a depressant action on the cerebrum, all caused either an absolutely stuporous state or at least a condition in which there was a marked reduction of responsiveness. Whilst many of these agents are primarily cerebral depressants, some of them are stimulants (e.g., carbon dioxide), and have a depressant action only when given in large doses. Administration of small doses results in a state of cerebral stimulation and the reflex cannot be elicited. The remaining seven drugs have either a stimulating effect on the cerebrum or a limited peripheral action.

The twenty-three drugs used in these experiments are listed in Table I, together with the following data: the method of administration and dosage per animal; a record of the presence or absence of the reflex; the time in seconds during which it occurred; and the longest single response recorded in each experiment. It will be noted that with the exception of bulbocapnine, all of the drugs were given in doses very large in proportion to the size of the animals. Only one animal was lost during the entire series of experiments; that was due to the effect of camphor. A wide range of variation in response to the different drugs is at once apparent from the table. These variations are brought out more clearly in the following charts.

After the administration of bulbocapine, the reflex quickly reaches maximum strength and then gradually decreases until it disappears entirely. The bulbocapnine curves are consistently very smooth and regular, as may be seen in fig. 1 A, in which the strength of the reflex as measured by the hanging time in seconds is presented on the ordinates and the duration of the experiment in minutes on the abscissæ. Before the injection (50 mg. of bulbocapnine) the hanging

response was absent; twenty minutes afterwards the response had reached a maximum for both hands, and fifty-five minutes later still it had entirely disappeared again.

TABLE I.

Agent	Mode of administration	Dosage per animal	Reflex present	Greatest interval in minutes during which hanging response was present	Longest hanging time in seconds
1. Bulbocapnine..	Subcut. inject.	10-100 mg.	+	450	92
2. Carbon dioxide	Inhalation	15-50 % 2-10 minutes	+	45	90
3. Ether	Inhalation	3 minutes	+	5	83
4. Amytal ..	Intraper. and intraven. inject.	0·5-1·5 c.c. 10 % sol.	+	320	57
5. Chloral hydrate	Intraper. inject.	500 mg.	+	240	2
6. Paraldehyde ..	Stomach tube	2·5 c.c.	+	420	65
7. Luminal ..	Subcut. inject.	530 mg.	+	320	8
8. Morphine ..	Subcut. inject.	34 mg.	+	120	6
9. Apomorphine ..	Subcut. inject.	17 mg.	+	20	20
10. Cocaine ..	Subcut. inject.	30 mg.	+	12	15
11. Hyoscine ..	Subcut. inject.	10 mg.	+ ?	100	10
12. Alcohol ..	Stomach tube	50 c.c. 50 % sol.	+	320	30
13. Insulin.. ..	Intraven. inject.	12 units	+	60	41
14. Camphor ..	Subcut. inject.	10 c.c. 20 % sol.	+	480	61
15. Eserine ..	Subcut. inject.	2·5 mg.	+	100	23
16. Strychnine ..	Subcut. inject.	2·2 mg.	+	30	9
17. Adrenalin ..	Subcut. inject.	2 c.c. 1 : 1,000	—	0	0
18. Atropine ..	Subcut. inject.	2·3 mg.	—	0	0
19. Pilocarpine ..	Subcut. inject.	6 mg.	—	0	0
20. Pituitrin ..	Subcut. inject.	2 c.c.	—	0	0
21. Caffein.. ..	Subcut. inject.	120 gr.	—	0	0
22. Nitroglycerine .	Subcut. inject.	1·4 mg.	—	0	0
23. Histamine ..	Subcut. inject.	12 mg.	—	0	0

Inhalation of carbon dioxide had much the same effect, but for a shorter length of time—a fact to be expected, since the carbon dioxide was administered in gaseous form and could thus escape more readily from the body. In fig. 1 B, it can be seen that the effect reached a maximum of sixty-five seconds, but persisted for only five minutes, in comparison to ninety minutes under the influence of bulbocapnine. A similar record, obtained during ether anæsthesia, is presented in fig. 1 C.

Alcohol produced a somewhat different type of curve. In fig. 2 A it can be seen that the reflex was present for four hours, remaining fairly constant throughout the entire time, but it never reached a level as high as with bulbocapnine, carbon dioxide, or ether.

Paraldehyde gave still another type of record, with the reflex very strong occasionally, but fluctuating widely from moment to moment, and sometimes actually difficult to elicit. A fairly typical record is presented in fig. 2 B. This animal received 2·5 c.c. of paraldehyde.

The records obtained after injection of amytal are interesting because of the light they may possibly throw on the relation of the reflex to sleep. In a typical experiment recorded in fig. 2 C, the reflex

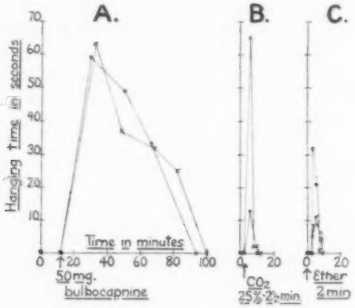

FIG. 1.—Graphs showing the effect of (A) bulbocapnine; (B) carbon dioxide gas, and (C) ether on the hanging response. The magnitude of the response in seconds is indicated on the ordinates, the duration of the experiment in minutes on the abscissæ.

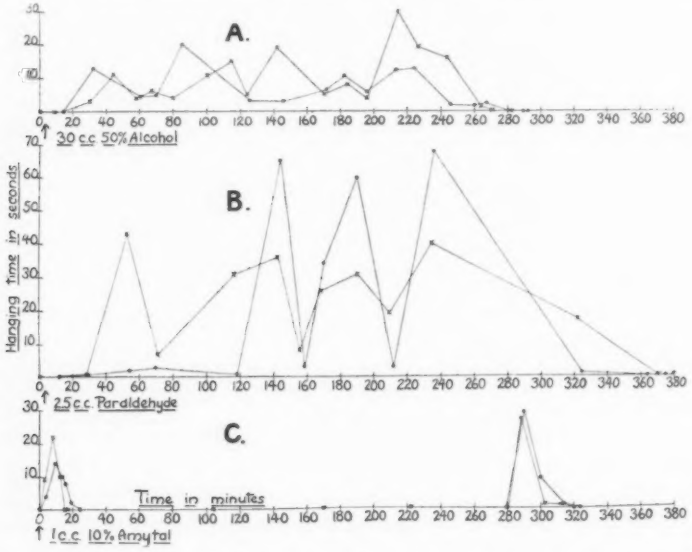

FIG. 2.—Graphs showing the effect of (A) alcohol; (B) paraldehyde, and (C) amytal on the hanging response.

was entirely absent during the sleeping period, lasting four hours, but was present for a short time, first before the animal fell asleep, and again for a while during the waking period.

For purposes of the discussion at hand, the above records will suffice. They all show that the reflex is always present in the state aroused by cerebral depressants. However, these drugs produce wide quantitative variations in effect, which it will be of considerable interest to investigate later.

Discussion.

Since the site of action in the brain is not known for the various drugs used in the above experiments, it is not possible at the present time to determine definitely how these drugs bring out the grasp reflex in adult animals. Some light, however, can be obtained from the following considerations. It has been established through the observations of Janischewsky, Schuster and many others that tumours or other lesions of the frontal lobes in man cause the reflex to appear. As has been frequently suggested, this must mean that under normal conditions the reflex is inhibited by impulses which have their origin in the parts of the brain affected or destroyed by the lesions. The evidence at hand indicates that the reflex mechanism itself must be located fairly far down in the brain-stem, probably in the region of the red nuclei (Minkowski, 1928; Troemner, 1928). The reflex could be brought out, then, either by a lesion or paralysis of a special part of the frontal lobe, or by severance of the connection between these lobes and the reflex centres in the stem. On this basis it may be assumed, for the moment, that the depressants described above paralyse the mechanisms in the frontal lobes, block the pathways from the frontal lobes to the motor centres in the cortex, particularly the occipito-frontal bundle of Schuster and Caspar, or block the pathways from the lobes to the lower centres. That the frontal lobes are involved would seem to be indicated by the fact that the animals are usually stuporous when the reflex is present. That the drugs must attack the nervous system also at a fairly low level is suggested by the observation that the reflex is brought out by hypnotics which are thought to act chiefly on the sleep mechanism in regions around the third ventricle. The results of the experiments with amytal and the other hypnotics are worthy of consideration in this connection, although their significance is not at all clear.

Summary.

(1) The grasp reflex can be brought out in adult monkeys by several pharmacological agents: bulbocapnine, carbon dioxide, ether, chloroform, amytal, paraldehyde, alcohol, luminal, hyoscine, cocaine,

morphine, apomorphine, camphor, insulin, chloral hydrate, eserine, and strychnine.

(2) All of these agents in the large doses given are cerebral depressants and have a definite effect on the responsiveness of the animals, producing a dazed or stuporous condition.

(3) Seven drugs failed to bring out the reflex: adrenalin, atropine, pilocarpine, pituitrin, caffein, nitroglycerine, and histamine.

(4) All of these drugs in the doses given act as cerebral stimulants, or peripherally, without affecting the central nervous system to any marked degree.

(5) It is suggested that the drugs which bring out the reflex must either paralyse the frontal lobes or block the inhibitory impulses in the pathways from the frontal lobes to motor regions or to the reflex mechanism in the brain-stem.

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CATAPLEXY.

BY MAX LEVIN.

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By cataplexy—a term first used by Henneberg—is meant the episodic occurrence of tonelessness, generalized or localized, as a reaction to an emotional stimulus (usually laughter). During the attack there is no impairment of consciousness, the cataplectic attack differing in this respect from the "Lachschlag" of Oppenheim.

Commonly the patient, while laughing heartily, suddenly becomes toneless, as a consequence of which, if standing, he falls, or, if seated, droops forward. Objects are dropped from the hand. The jaw drops, but relaxation of the sphincters rarely occurs. For from several seconds to several minutes the patient cannot move, after which he suddenly regains complete control of his musculature. Less frequently cataplexy is localized, being confined to the jaw or one or more of the extremities.

Emotions other than laughter that have brought on cataplectic attacks are the joy and surprise of unexpectedly meeting an old friend on the street; the excitement of receiving a good hand at cards; the emotion associated with orgasm; the unpleasant emotion of a father about to spank his child. In Holmes' patient attacks occurred when he was startled, as by the sound of a tire bursting or on being silently overtaken by a cyclist.

In some cases there seems to be a relation between the intensity of the emotion and the severity of the cataplexy. Thus, in Case 2, recorded in my recent paper, hearty laughter led to profound tonelessness of the jaw, neck, arms and shoulders, while the mildly unpleasant emotion incident to leaving a warm comfortable bath resulted merely in a slight relaxation of the jaw. Similarly, in Case 3, in the same paper, the patient on hearty laughter was overcome by generalized tonelessness, so that his knees sank, his arms dropped, and his head fell either forward or backward. On the other hand, if, while holding and reading a newspaper, he came across a familiar statement, the resulting mildly pleasurable feeling led merely to a slight hypotonia in the arms, so that

involuntarily he lowered the paper an inch or two; sometimes, on such occasions, without perceptibly lowering the paper, he became aware of a sense of relaxation in his arms.

The literature contains sixteen cases in which the opportunity presented itself to examine the patient *during* the cataplectic attack (Jacobssohn; Gillespie; S. A. K. Wilson, Case 2; Worster-Drought; Stewart; de Villaverde; Ratner, Case 2; Martin; Zehrer, Case 3; Bromberg; Fröderberg; Wagner, Case 1; Serejski and Frumkin, Case 1; Cave, Cases 17 and 24; and Silverstein). In nine instances the muscle tone was noted, being always diminished or absent. Ten authors report on the deep reflexes: eight found them absent or diminished, one found them normal (Fröderberg), and one noted them as present (Bromberg). The response to plantar stimulation was observed in four instances: in two cases it was normal; in Stewart's case the plantar reflexes were "either absent or indefinite"; in Wilson's case there was a "slight but definite" extensor response. The condition of the pupils was noted in eight cases: in two (Ratner; Serejski and Frumkin) they were small and did not react to light; in both of Cave's cases they were noted as small, but no mention was made of their reaction to light; in Martin's case they were dilated and did not react; in the remaining three cases (Gillespie; Wilson; de Villaverde) they reacted to light, but the size was not mentioned.

The overwhelming majority of patients with cataplexy complain also of episodic morbid somnolence—a combination of symptoms to which the term narcolepsy, or Gélineau's syndrome, is applied. According to my count, over 180 cases of Gélineau's syndrome have been recorded. On the other hand, of patients suffering from cataplexy but free of morbid somnolence, only fourteen have been recorded (Symonds; Holmes; S. A. K. Wilson, Case 5, and an unnumbered case on page 95; Rosenthal, Case 7; Rothfeld; Münzer; de Villaverde; Ratner, Cases 4 and 7; Martin; Tsiminakis, Case 1; Wagner, Case 2; and Fouché). Cohen made brief mention of a case of spastic diplegia with cataplectic attacks; nothing was said of morbid somnolence, and one infers that it was absent.

It is my purpose here to record two recently observed cases of "cataplexy only."

Report of Cases.

Case 1.—*Coloured girl. Two cataplectic attacks during her 16th year. Subsequently two types of attack occurred:* (1) *falling attacks occurring independently of emotional stimuli, and* (2) *attacks of unconsciousness without*

convulsions. At 17, tremor of the right arm, later limiting itself to the right hand and present also during sleep developed.

An intelligent coloured girl, aged 17, first came under my notice on July 10, 1930.

Past history.—She had always been frail, having had three attacks of pneumonia during the first six years of life. At 12 she began to complain of intermittent aching of her various joints. At 15 she began to have fleeting precordial pains and dyspnœa. She tired readily. At 16 she began to have intermittent swelling of both ankles, without pain or redness.

At 15 years and 10 months the first menstrual period occurred. The periods were usually six weeks to two months apart. The patient was never aware of sex desire and had never had coitus: in this respect she was unique among her friends.

Cataplexy.—The first neurological symptom was a cataplectic attack occurring several months prior to the first menstrual period. The patient was standing talking to her sister and laughing heartily. In the midst of a sally of laughter she dropped without warning to the floor. On the floor she was able to attain the sitting posture and to move her legs a little, but was unable to get up. There was no disturbance of consciousness, and she neither wet nor soiled herself. She was chagrined over this unheard of type of disability, and her laughter gave way to tears: "I didn't know why I had gotten weak all of a sudden, without any cause—just from laughing." After five minutes the patient was able to get up, and then felt perfectly well.

Six months later another attack occurred, an exact duplicate of the first. No further cataplectic attacks occurred, in spite of the fact that she frequently laughed. On such occasions there was not even a feeling of weakness.

"*Falling attacks.*"—During the six months following the second cataplectic attack (i.e., from June to December, 1929), the patient had twenty or more "falling attacks" occurring independently of emotional experience. They occurred, for example, while she was out walking by herself. Since she worked long hours in a hair-dressing establishment, standing most of the time on her feet, she was inclined to attribute the attacks to fatigue.

Attacks of unconsciousness.—In the autumn of 1929 the patient began to have infrequent attacks of unconsciousness, unassociated with self-injury, convulsions, biting of the tongue, or relaxation of the sphincters. At first these occurred only at her place of employment, and she ascribed them to the heat of the hair-drying machine near which she worked. In May, 1930, two attacks occurred under altogether different circumstances. (1) One Sunday morning, in church, while walking down the aisle to her seat, she suddenly fell unconscious, remaining so for several minutes. (2) A few weeks later, again at a church service, a quarrel arose between the pastor and one of the members of the congregation. Presently the latter advanced menacingly down the centre aisle to the pulpit, and great excitement spread through the congregation. The effect of this was to make the patient feel "nervous and shaky," and she decided to leave. Inasmuch as she was sitting in the front row of the

balcony, she had to ascend about ten steps to reach the aisle leading to the exit. On the third or fourth step she fainted, regaining consciousness in the accident ward of a nearby hospital.

Subsequent to December, 1929, the patient had no further "falling attacks," and but two attacks of unconsciousness (these being the two in church).

"*Nervous breakdown.*"—On January 1, 1930, the patient had a "nervous breakdown." Having been out very late the night before, she took a fifteen-minute nap in the early evening, from which she awakened feeling "really sick: my heart was paining, I couldn't get my breath; my heart felt to me as if it was coming out of my body. I was shaking all over. I felt nervous and wept." In an hour the generalized tremor subsided, but there remained a tremor of the right arm that persisted for six weeks. For a time this was so marked that she was unable to feed herself with the right hand. The tremor of the right arm was replaced by a tremor of the right hand, which was still present when I saw the patient.

Upon careful questioning it was ascertained that there was no history of morbid sleepiness.

Physical examination.—The patient was slender, being 63 in. (160 cm.) tall, and weighing 108 lb. (49 kg.). The right lobe of the thyroid was slightly enlarged. The heart was not enlarged. There was a loud systolic murmur. The pulse-rate varied from 80 to 90. The blood-pressure was 146 systolic, and 70 diastolic.

The right arm was slightly weaker than the left. There was a marked tremor of the right hand, present even when the hand was at rest. Her relatives observed that it was also present during sleep. There was a faint, almost imperceptible tremor of the outstretched fingers of the left hand. The finger-nose test showed moderate ataxia, more so on the right. Alterations of tone were not apparent on passive motion. The results of the examination were otherwise without significance.

Laboratory examinations.—The blood-counts were normal. The Wassermann reaction of the blood and spinal fluid and the colloidal gold curve were negative (other spinal fluid examinations were not made). The basal metabolic rate on two occasions was minus 4 per cent. and plus 6 per cent. A roentgenogram showed a normal sella turcica.

To summarize, the patient presented three groups of symptoms: (1) Rheumatic-arthritic-cardiac symptoms: joint pains for the past five years; fatigue, dyspnœa and precordial pains for the past two years: swelling of the ankles for the past year; signs of mitral insufficiency. (2) Evidence suggestive of gonadal inadequacy; delayed puberty and deficient libido. (3) Nervous symptoms: a cataplectic attack one and a half years ago, followed by a similar attack six months later; during the ensuing six months, over a score of "falling attacks" occurring independently of emotional stimuli; during the past nine months a

number of attacks of unconsciousness, one of which occurred during an exciting episode in church; a "nervous breakdown" six months ago, characterized by an episode of acute anxiety and generalized tremor, leaving in its wake a tremor of the right arm lasting six weeks, which was in turn succeeded by a tremor of the right hand. At present marked tremor of the right hand (present also during sleep); an almost imperceptible tremor of the fingers of the left hand; slight weakness of the right arm; no disturbances of tonus. The patient was under my observation for several months, during which the tremor of the right hand remained unchanged. The only treatment consisted of the oral administration of potassium iodide. I lost sight of her when she moved to another city.

Comment.—The interest in this case lies in the evidence pointing to the possibility of a striatal lesion—a virtually unilateral tremor, present also during sleep. This possibility is enhanced by the presence of rheumatic cardiac disease, since there is increasing acceptance of the view that the chorea often associated with rheumatic disease is dependent on a lesion of the striatum [7]. At the same time the evidence of striatal disease in the present case is far from conclusive, since (except during the two attacks of cataplexy) changes in tonus were absent.

Evidence suggesting the possibility of a striatal lesion in a patient with cataplexy is of more than usual interest. Several authors have suggested in recent years that the striatum might play a role in the production of cataplexy. Thus, Redlich emphasizes the tone-regulating function of the striatum, pointing out that in destructive striatal lesions there is interference with the tone-inhibiting centres, resulting in hypertonia. He suggests that an opposite process occurs during lively emotions, leading in extreme instances to the hypotonia of cataplexy. He confesses that the matter is still unsettled, but he feels that the process is functional rather than anatomical; he speaks of it as "a disturbance of the equilibrium of the subcortical centres."

Rothfeld has made a noteworthy suggestion based on the assumption that the tone-inhibitory globus pallidus is itself normally inhibited by the neostriatum, and that both of these structures are capable of being inhibited by the thalamus. He contrasts the external manifestations of sad and gay emotions: a man following a hearse is bowed down with grief, his face is rigid, and there is paucity of associated arm movements on walking—an akinetic-hypertonic picture; on the other hand, a lad following a military band carries himself erect, swings his arms briskly, and displays lively facial mimicry—a hyperkinetic-hypotonic picture.

The hypotonic phenomena associated with happy emotions are even more conspicuous in laughing children, who have not yet learned to inhibit the free expression of their moods. The akinetic-hypertonic (sad) picture is regarded by Rothfeld as a manifestation of inactivity of the tone-inhibitory pallidum; the hyperkinetic-hypotonic (happy) picture suggests, on the other hand, a temporary suspension of the pallidum-inhibitory function of the neostriatum, as a result of which the pallidum is for the moment permitted to function without restriction. Rothfeld therefore proposes that laughter be defined as a reaction which occurs when cheerful stimuli "affect the subcortical ganglia in such a way that the thalamus releases inhibitory impulses which restrict the regulative effect of the neostriatum on the pallidum." Under suitable conditions this process may be exaggerated to the point where tonelessness, i.e., cataplexy, results.

We still know too little about the striatum to be dogmatic. Nevertheless, the relative frequency of Gélineau's syndrome in patients with the Parkinsonism of epidemic encephalitis lends probability to the assumption that the striatum is in some way involved in the mechanism of cataplexy. This probability is enhanced, if only slightly, by the case here reported. It is well to remember that so far there has been no necropsy in a patient with cataplexy.

While ordinarily Gélineau's syndrome and epilepsy occur separately, there are occasional cases containing features of both. Thus Grainger Stewart's patient was an epileptic who later developed cataplectic attacks and, still later, sleep attacks. Conversely, Holmes' patient, who had cataplexy but no sleep attacks, later developed epilepsy. In view of this occasional association it is noteworthy that our patient had attacks of unconsciousness, though without convulsions. The continuous tremor of her hand is similar to a phenomenon described by Kojevnikov under the name epilepsia partialis continua: continuous muscular twitchings occurring in any part of the body, without impairment of consciousness, in the intervals between major epileptic attacks [28].

A lesser point of interest is that our patient is coloured. But two other cases of negroes with cataplexy have been reported, both of them being cases of Gélineau's syndrome (Thrash and Massee; Wahl).

Case 2.—White male, of a manic-depressive disposition. Manic attacks at 16 and at 18. Beginning at 15 or 16, attacks of cataplexy localized in the right arm and hand. Beginning at 18, attacks of unconsciousness apparently of an epileptic nature.

An intelligent young white man began at 14 to have wide variations of

mood, alternating between gloominess and exhilaration. At 16 he had a manic excitement, lasting three or four months. He made a good recovery. At 18 he had a second manic attack, lasting two weeks. During the second week of this attack, on August 25, 1931, he was admitted to the Harrisburg State Hospital. Five days after admission the attack subsided, and thereafter he showed no further mental symptoms.

Cataplexy.—The patient was "high-strung" and trembled when under tension, e.g., when presented to the medical staff. In discussing this difficulty he revealed that for two or three years he had been having attacks of inadequate control of his right arm and hand. (He was right-handed in everything he did.) Frequently these attacks were precipitated by excitement. For example: (1) It frequently happened that in the midst of an exciting volley at tennis his racquet dropped from his hand; in less extreme instances he was able to hold on to the racquet, but it wobbled to such an extent that he was unable to play the ball accurately. (2) On several occasions, while playing an exciting game of cards, he suddenly lost control of his right hand in which he was holding the cards, with the result that "I sort of sprawled the cards." (3) An instructive episode occurred at the age of 15 or 16. The patient was employed as an errand boy in a grocery store. One morning, returning from having delivered several orders, he turned his money over to his employer (a woman). She called his attention to the fact that he was ninety-six cents short. As an old friend of his family, she knew him well and did not question his honesty; she felt rather that he had erred in giving change to one of the customers. The patient was painfully embarrassed. Ten minutes later she gave him another order to deliver. He placed the basket on his right arm and started to leave. "As I was about to open the door, my right arm shook and brought the basket down to my wrist." The attack was sufficiently brief to permit him to recover the basket with his right hand.

Less frequently the symptom occurred in situations free of excitement. For example: (1) While he was writing the fountain-pen occasionally slipped from his hand. Sometimes, without dropping the pen, he found himself momentarily unable to guide it properly. (2) During his convalescence at the hospital he noted on several occasions, while drinking coffee at breakfast, that his right arm trembled. On three occasions this was so severe that some coffee was spilt, but the cup was never dropped.

An invariable characteristic of the attacks was that they lasted but a few seconds and were not accompanied by disturbance of consciousness. As regards the tone of the arm during the attack, the patient stressed the fact that his arm was "weak"; it never "drew up," nor did he use any of the other terms used by laymen in describing a Jacksonian fit. The phenomenon never occurred during laughter. It never involved any part of the body other than the right arm and hand.

The patient never suffered from morbid somnolence.

Examination.—The patient was well developed. The examination showed no abnormalities, save a moderate tremor of the tongue and outstretched fingers.

Attack of unconsciousness.—On October 27, 1931, for the first time in his life, the patient fell unconscious. He was sitting in the day-room of the ward, playing checkers with a fellow-patient. Without warning he lost consciousness and was laid on the floor, where he lay quietly for twenty minutes before coming to himself. There were no convulsions, nor were the bladder and bowels evacuated. No physician saw him at the time.

The patient was given parole on November 5, 1931. During the ensuing five months he had four attacks of unconsciousness, in some of which he showed definite tonic and clonic spasms. He had numerous attacks of cataplexy.

Comment.—The limitation of the cataplexy to the arm and hand is noteworthy.

Since patients with cataplexy react unfavourably to strong emotional stimuli, the circumstances surrounding the onset of the second manic attack are remarkable. The patient and an uncle went on a ten-day motor tour. On the way home the uncle provided himself with a large quantity of strong liquor, which he consumed freely. Since the patient does not drive, he was forced to entrust himself to his intoxicated uncle, and throughout the remainder of the trip he was filled with dread. The manic attack began while he was in this state of mind; on reaching home he was already over-talkative and elated.

In view of the occasional association, already alluded to, of the phenomena of epilepsy and those of Gélineau's syndrome, the attacks of unconsciousness are noteworthy. For the same reason, the family history is significant. The father, a civil engineer, a robust man of unusual intelligence, began at 17 to have *petit mal* attacks. From 17 to 20 he took a difficult course at a German technical school. During this period he was under great strain, and the attacks were frequent. Graduation at 20 was accompanied by a sense of profound relief. Thereafter the attacks occurred but infrequently. He never had a *grand mal* attack or a cataplectic attack. A paternal great-aunt and a maternal uncle had major epilepsy.

Summary.

Two cases of cataplexy are presented. Neither patient had morbid somnolence. In addition to cataplexy, both patients had attacks of unconsciousness. The first patient had a constant unilateral tremor, present also during sleep, suggesting the possibility of a lesion of the corpus striatum.

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THE STRUCTURE AND CONNECTIONS OF THE THALAMUS.[1]

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JUST over twenty years ago, in the Arris and Gale lectures which he delivered on the subject of the evolution of the cerebral hemispheres, Elliot-Smith [16] expressed his opinion that the key to the interpretation of the structure of the rich cortical component of the cerebral hemispheres which is found in mammals—the neopallium—lies in an intensive study of the thalamus. For it is well known that, with the solitary exception of olfactory impulses, all sensory impulses which are destined to reach the cerebral cortex have first to be filtered through the mass of grey matter which is found in the walls of the third ventricle, the optic thalamus. From the thalamus such sensory impulses are projected on to the cortex by thalamo-cortical fibres, and their mode of distribution to topographical cortical areas is no doubt determined in large part by the spatial relationship of the thalamic nuclei from which these fibres arise. This fundamental fact has been emphasized by several anatomists (von Monakow [43], Cajal [5], Elliot Smith [16]), and rests on the observation that projection fibres usually take the most direct and shortest route from the thalamic centres to the cortex. Not only does the thalamus in this way determine a spatial localization in the cortex, but it is possible for sensory impulses on their way through the thalamus to undergo modification and selection as the result of being brought into relation with the activities of intrinsic thalamic mechanisms. In other words, the neopallium must depend entirely on the thalamus for the precise nature of the sensory material which it receives indirectly from peripheral receptors. It is true that there is evidence to indicate that cortical mechanisms can modify thalamic activities by inhibitory influences, but the fact remains that, so far as the purely sensory functions of the neopallium are concerned, the latter from the developmental and functional point of view is to be regarded as a dependency of the thalamus and not *vice versa*. This

[1] The material of this paper formed the basis of two Arris and Gale lectures delivered at the Royal College of Surgeons on February 17 and 19, 1932.

consideration further emphasizes the necessity of a sound knowledge of intrathalamic connections before it is possible to gain a fuller appreciation of the part played by the highest functional levels of the brain in the working of the mind.

But the thalamus is much more than a relay station for the passage of sensory impulses on their way to the cerebral cortex. Into the thalamus there come fibres conveying sensory impulses of every possible kind, somatic and visceral, impulses which convey intimation of changes within the organism itself and of changes in the external environment. Here, long before the neopallium has appeared in evolutionary history, a mechanism is provided for the interaction and blending of these diverse afferent impulses, and, in relation to this plain anatomical fact, it may be noted that there is accumulating evidence based on clinical and psychopathological observation that the thalamus is the anatomical equivalent of the very threshold of consciousness.

Thus it is clear that a study of thalamic structure and function is of the highest importance in connection with fundamental problems of neurology and of normal and abnormal psychology.

It is curious that less should be known of the intrinsic structure and connections of the thalamus than perhaps of any other part of the brain. While a great deal of attention has been focused on the cerebral hemispheres above and the brain-stem below, the "Zwischenhirn" or between brain, which forms such an essential link between the two, has only comparatively lately begun to be submitted to a really intensive scrutiny. There are two main reasons for this neglect of thalamic anatomy. One is the confusion of nomenclature and the lack of definition which occur in the literature of the subject, and which have repeatedly led to misconceptions and misinterpretations which it has been impossible to harmonize with one another, and the other is the difficulty of applying the usual experimental methods to this part of the brain. It is clear, however, that the experimental method can be of little avail without a satisfactory definition of the elements which are to be subjected to study and, indeed, much of what little experimental work has hitherto been done on the thalamus has been vitiated by the neglect of a preliminary and detailed anatomical study. One of the main objects of this paper is to clear the terminological atmosphere so as to provide a sound anatomical basis for future investigations on the thalamic functions.

The thalamus in higher mammals becomes such a complicated structure that it is well-nigh impossible to unravel its complexities by direct anatomical methods. It is essential, in order to define the funda-

mental elements of its composition, to study it in the more simple form in which it is found in small and generalized mammalian types. Then, by a study of a closely graded series of mammalian brains from a comparative anatomical point of view, arranged to correspond as nearly as may be to a true phylogenetic series, it is possible by direct comparison to trace the changes which occur in the development of the more complex from the more simple type of thalamus, and to establish satisfactory homologies of its component parts. Thus, for instance, the nuclear elements of the thalamus of lower mammals may, in this manner, be indirectly compared with those of the human brain, and the way prepared for a satisfactory correlation of clinical observations with the results of physiological experimentation. To institute a comparison between the thalamus of man and the thalamus of a specialized mammalian type such as the dog or cat, without reference to intermediate forms, may lead to fallacious interpretations.

This method of comparative anatomy is a necessary preliminary to any detailed study of the thalamus. As regards the experimental approach, although the method of tracing degenerated fibres by Marchi staining has been applied by several investigators to the study of extrinsic and intrinsic thalamic connections, it has hitherto led to comparatively meagre and uncertain conclusions, partly due to the lack of a precise anatomical study of normal material, but partly due to the fact that the initial lesions have usually not been sufficiently circumscribed. Judiciously used, the Marchi method promises to supply much information. The interpretation of its results so far as it has hitherto been applied to the thalamus has been rendered often difficult because the severity of the lesion has introduced complicating factors. Much of the current anatomical description of thalamic connections is based on degeneration after severe lesions of the brain, and for this reason should be regarded very critically. It is essential to be content with the production of very small and localized lesions, and to make a complete series of serial sections of the material in order accurately to delimit the extent of the lesion and to trace degenerating fibres in continuity to their termination. The greatest care must also be used to distinguish between fibres of passage and those which are directly connected with thalamic nuclei. Large numbers of such records are required and only by prolonged and tedious research will it be possible to complete a survey of the thalamus in this way.

References are made in the course of this paper to some experimental work which the author has carried out on the thalamic connections in

the rat's brain. A detailed account of this study will be found elsewhere [12].

The General Terminology of the Diencephalon.

There is much lack of agreement regarding the terminology even of the main parts of the diencephalon. That which will be adopted here may conveniently be indicated by referring to the diencephalon of the human brain as it appears during the third month of fœtal development.

Viewed from the ventricular aspect the lateral wall of the third ventricle shows a relatively large rounded swelling which represents the thalamus *sensu stricto*. Below the thalamic eminence is a well-defined groove called the sulcus hypothalamicus which extends forwards from the region of the aqueduct of Sylvius to the optic recess. This sulcus, it has been suggested, represents the anterior prolongation of the sulcus limitans of the embryonic neural tube which separates the sensory lamina from the motor lamina. This, however, is too doubtful to form the basis of any inferences regarding the functional level of those parts of the diencephalon which lie in relation to it. The more recent embryological studies indicate, indeed, that the basal lamina does not extend further forward than the mid-brain. The hypothalamic sulcus, however, serves to mark the division of the diencephalon into two main parts, the significance of which it is important to recognize. Above the level of the sulcus is the *pars dorsalis diencephali* which consists of the thalamus proper and, above this, the epithalamus. Below the sulcus is the *pars ventralis diencephali* which consists of the hypothalamus and the subthalamus. The epithalamus is represented by the pineal diverticulum from the roof of the ventricle and an elongated swelling which stretches back from the region of the interventricular foramen to the base of the diverticulum. This swelling indicates the position of developing groups of nerve-cells and fibre systems which are intimately related to the olfactory parts of the cerebrum and which, on the basis of comparative anatomy, appear to arise primarily in connection with the pineal organ or epiphysis. The thalamus forms by far the greater part of the pars dorsalis diencephali except in the most primitive vertebrates, and it is to be regarded as a great sensory ganglion which receives all varieties of somatic sensory impulses. In higher forms it represents an essential link on the afferent side between the neopallium and lower levels of the central nervous system. The geniculate bodies (which receive terminals of the auditory and visual tracts) are sometimes separated descriptively from the thalamus proper and grouped together

as the metathalamus. This term, however, seems superfluous, for the geniculate bodies are both outgrowths from the main sensory nucleus of the thalamus.

The hypothalamus consists of a glandular outgrowth from the floor of the third ventricle (the pars nervosa of the pituitary gland) and a series of nuclear masses which develop in topographical and functional relation to it. In this region the optic chiasma is situated and, with certain other decussations, becomes included as a part of the hypothalamus. Lateral to the hypothalamus, and not extending medially as far as the ventricular wall, is the subthalamus, which may be regarded broadly as the pathway of all the elements of the lateral fore-brain bundle which pass from the cerebral hemispheres to lower levels and link up the cortex and basal ganglia with the brain-stem and spinal cord. It is bounded medially by the hypothalamus, above by the thalamus proper and the termination of the medial fillet, and its ventro-lateral margin is formed by the cerebral peduncle or pes pedunculi. Among the fibre tracts which pervade it are a series of nuclear masses (such as the entopeduncular nucleus, the subthalamic nucleus of Luys, the diffuse cell groups of the zona incerta) which form links in a broken chain of nuclear structures connecting up the corpus striatum above with the grey matter in the tegmental region of the mid-brain below (e.g., the red nucleus, substantia nigra, reticular nuclei). The nuclei of the subthalamus form in large part a series of relay stations for fibres which descend from the striatum, and constitute essential elements in the so-called extra-pyramidal motor system. They are also intimately related to the elements of the hypothalamus medially by fibre connections, and there is no doubt that they receive the terminations of certain afferent paths.

This nomenclature of the main parts of the diencephalon is not in accord with that adopted by American neurologists in general (e.g., Herrick [25] and Huber and Crosby [31]), who call the subthalamus the "ventral thalamus," while the term "dorsal thalamus" is reserved for the thalamus proper.

Evolution of the Thalamus.

The relations and general significance of the main subdivisions of the diencephalon may conveniently be indicated by referring to its evolutionary history. The evolutionary development of the diencephalon throughout the vertebrate series is manifested by a progressive elaboration of its dorsal part, and this is apparently contingent at first upon

the termination of an increasing number of direct and indirect sensory paths in it and, later, upon the reciprocal relation which develops between the thalamus and the superposed neopallium. Thus when the diencephalon is followed through a descending series of vertebrates the thalamus proper shrinks, while the epithalamus and the hypothalamus become increasingly important elements respectively. In the most primitive vertebrates, the cyclostomes [26, 27, 56], the thalamus is little more than a slender band of nervous tissue running dorso-ventrally and linking up the epithalamus above with the hypothalamus below. The afferent paths which reach it from the brain-stem and spinal cord without being relayed through the tectum are so small that we are led to the conception of a protean type of vertebrate brain in which somatic impulses reach the diencephalon entirely through tectal connections. Such a type of brain is represented in the accompanying diagram (fig. 1A). The epithalamus comprises the pineal organ and a mass of nerve-cells at the site of its attachment to the roof of the third ventricle, the habenular ganglion, or habenula. The hypothalamus forms a conspicuous swelling in the floor and lower part of the lateral wall of the ventricle and lies in direct relation to the pituitary gland. Both the habenula and the hypothalamus receive rich contributions of fibres from the telencephalon, which is entirely olfactory in function.

It is convenient to draw attention at this point to a distinction in anatomical connections between the dorsal part of the diencephalon and the hypothalamus which seems to imply a fundamental functional contrast. The pars dorsalis diencephali (represented in the cyclostome brain practically entirely by the epithalamus and in higher forms incorporating the thalamus proper) is a sensory correlation station which receives impulses of a somatic nature, that is to say, impulses which are the result of stimuli produced directly by changes in the external environment, and through which motor reactions to these stimuli are ultimately rendered possible. In primitive vertebrates there are tecto-habenular connections by which visual and general sensory impulses, &c., are enabled to reach the habenula, and among its cells terminate the fibres of the pineal nerve which also certainly convey exteroceptive impulses, probably of a visual nature. The habenular ganglion thus provides a neural mechanism through which the organism may become aware of the varying conditions of its external environment and by which it can adjust its own behaviour so as best to adapt itself to these conditions. Such exteroceptive functions are essentially connected with the dorsal part of the diencephalon in all vertebrates.

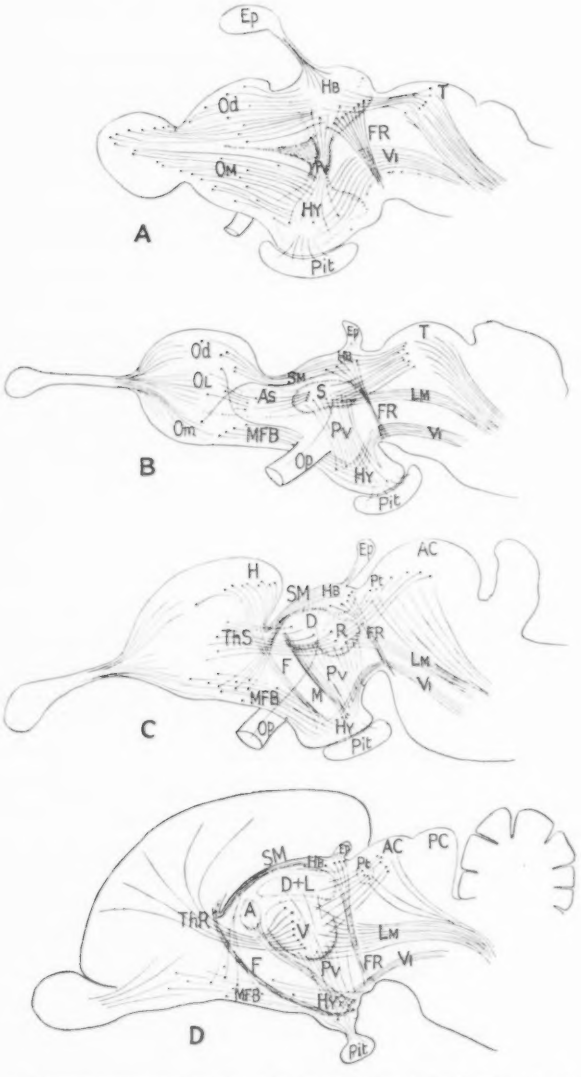

FIG. 1.—Diagrams representing stages in the evolution of the thalamus. *A*. Primitive cyclostome. *B*. Fish. *C*. Reptile. *D*. Mammal. *AC*. Anterior colliculus. *As*. Area somatica. *D*. Nucleus dorso-lateralis anterior. *D + L*. Nucleus dorso-medialis + nucleus lateralis. *Ep*. Epiphysis. *F*. Fornix. *FR*. Fasciculus retroflexus. *H*. Hippocampal formation *Hb*. Habenula. *Hy*. Hypothalamus. *LM*. Medial lemniscus. *M*. Mammillo-thalamic tract. *MFB*. Medial forebrain bundle. *Od*. Area olfactoria dorsalis. *Ol*. Area olfactoria lateralis. *Om*. Area olfactoria medialis. *Op*. Optic tract. *PC*. Posterior colliculus. *Pit*. Pituitary. *Pt*. Pretectal nucleus. *Pv*. Periventricular system. *R*. Nucleus rotundus. *S*. Main sensory nucleus of the thalamus. *SM*. Stria medullaris. *T*. Tectum. *ThR*. Thalamic radiations. *ThS*. Thalamo-striate fibres. *V*. Ventral nucleus. *Vi*. Ascending visceral tracts.

The hypothalamus, on the other hand, is a visceral correlation centre. In it there terminate fibres which arise from visceral nuclei in the brain-stem. This fact has been demonstrated by direct anatomical methods in the case of lower vertebrates in which the ascending visceral tracts are relatively conspicuous [34]. In higher vertebrates and man, the intimate relation between the hypothalamus and visceral centres has been corroborated by experimental and clinical evidence. This evidence indicates that the hypothalamus comprises a neural apparatus through which are controlled and regulated vegetative functions of the organism as represented by fundamental metabolic processes, endocrine activity, viscero-motor mechanisms, vaso-motor phenomena, &c. From this it may be inferred that the hypothalamus in mammals is certainly connected directly or indirectly with viscero-sensory nuclei in lower levels of the central nervous system as in lower vertebrates, and there is some anatomical evidence to confirm this proposition. The close relation between the hypothalamus and the pituitary gland has already been mentioned. That the two work together in the closest collaboration to form a unified neuroglandular mechanism is proved by anatomical and physiological observation. Some of the nuclei of the hypothalamus are directly related by nerve-fibres to both the anterior and posterior lobes of the pituitary, and the intimate vascular connections between the hypothalamus and the gland have recently been emphasized by the work of Popa and Fielding [49] who, working in Elliot Smith's laboratory, have described a portal circulation in the region of the tuber cinereum. In view of the part which the pituitary is known to play in controlling growth in fœtal and post-natal life, its dominating influence over the endocrine system generally, its power of regulating fundamental rhythms of sexual life and development, &c., it is not unreasonable to suppose that through its connections with the gland the hypothalamus provides a region of the brain in which the basic vital activities of the organism may be echoed in terms of neurogenic processes. These considerations lead to the suggestion that the hypothalamus is the recipient of those vague and undefinable impressions which arise in association with all sorts of visceral activities and metabolic processes, and which, in their totality, represent sensory material by which the organism is enabled to appreciate itself as a unified being, an individual existing as an organised entity, without special reference to the external environment. In general, then, the hypothalamus may be regarded as a part of the diencephalon which, by its nervous connections and through the direct liaison which it establishes with the hormonic regulatory system *via* the

pituitary, mediates the integration of visceral impulses and plays an essential part in the control of the internal milieu of the organism. Thus it stands in direct contrast to the functional implications of the dorsal part of the diencephalon. While the latter is the recipient of impulses on the basis of which the organism may develop an awareness of its external milieu and adapt its overt behaviour accordingly, the former is the recipient of impulses on the basis of which the organism may develop an awareness of its internal organic activities and through which sensory experiences are endowed with an affective tone.

In all vertebrates, the dorsal part of the diencephalon and the hypothalamus are linked together by a strand of cells and fibres which form what may be called the periventricular system. In the cyclostome brain this primitive connecting link is apparent as a narrow band lying vertically in the lateral wall of the third ventricle and connecting the habenula with the hypothalamus. Through this periventricular system the somatic correlation centres of the diencephalon are brought into functional relation with the visceral correlation centres. This provides a basic mechanism whereby the organism is enabled to equate consistently the impressions which it derives from the outside world with the organic functions of its own being.

In cyclostomes the whole diencephalon receives rich fibre connections from the olfactory centres of the cerebral hemispheres. Both the epithalamus and the hypothalamus, indeed, are directly continuous with the dorsal and medial olfactory areas without any clear line of demarcation.

In the brain of fishes (fig. 1 *B*), in association with an increasing proportion of somatic impulses entering the dorsal part of the diencephalon, the thalamus proper shows signs of incipient differentiation immediately below the epithalamus (Herrick [26]). In this way arises a part of the diencephalon which is not under the direct influence of olfactory impressions. It is said by some authorities that in certain teleostean types at least it is possible to trace a few olfactory fibres directly into the thalamus proper, but, if this is so, they are insignificant and rapidly disappear in the process of further evolutionary development. The thalamus receives its somatic impulses mainly through the tectum, but there is the beginning of a lemniscus system of sensory tracts from lower levels, and collaterals of the optic tract also terminate in it (as they also do even in cyclostomes according to Tretjakoff [56]). The thalamus is also beginning to push its influence forwards into the sphere of the telencephalon—to invade a territory

which was primarily a domain of the olfactory system. Here it leads to a differentiation of a region which has been called the area somatical and which is continuous anteriorly with the lateral olfactory area of the fore-brain. The area somatica is the precursor of the somatic part of the corpus striatum of higher forms. In fishes there is no clear boundary between the diencephalon and the telencephalon so far as intrinsic structure is concerned. The whole fore-brain can, indeed, be described as consisting of three longitudinal columns of cells of which the dorsal is represented by the dorsal olfactory area (precursor of the hippocampal formation) prolonged back without interruption into the epithalamus, the ventral by the medial olfactory area (precursor of the septal and parolfactory areas) and the hypothalamus, while between the two is another column comprising the lateral olfactory area, the area somatica and the thalamus proper. The fibre connections between the thalamus and the area somatica of the hemisphere represent the fore-runners of the strio-thalamic and thalamo-striate connections. It will be noted in the diagram that the dorsal olfactory area becomes related by efferent connections with the hypothalamus, and this marks the appearance of a fornix system which is first seen in the selachian brain. The medial olfactory area also sends fibres dorsally to the epithalamus, representing the olfacto-habenular component of the stria medullaris.

In the reptilian brain (fig. 1 *C*), a pronounced elaboration of the pars dorsalis diencephali may be observed (De Lange [36] and Crosby [30]). The thalamus proper has increased considerably in size and shows an intrinsic differentiation into fairly well-defined nuclear masses. Several thalamic nuclei have been described, but here attention may be especially directed to the two which make up the bulk of the somatic part of the thalamus, the nucleus dorso-lateralis anterior, and the nucleus rotundus. Both these are composed of similar types of cells and are not everywhere clearly separated from each other. Both are connected with somatic areas in the lateral part of the cerebral hemisphere. They receive afferent impulses through tectal connections, and the nucleus rotundus, at least, is believed to receive lemniscal fibres. Together they represent the main somatic sensory centre of the diencephalon, equivalent to the "pars dorsalis diencephali" of amphibia as defined by Herrick [25], and to the ventral group of nuclei, the main part of the nucleus anterior, the dorsal nucleus of the lateral geniculate body and probably the medial geniculate body of mammalia (*vide infra*, p. 433). The nucleus rotundus is a very distinctive element in the sauropsidan thalamus. That it represents a part of the ventral group of nuclei of the mammalian

thalamus (possibly the nucleus medialis ventralis) is almost certain. It is equally certain, however, that its size and marked differentiation is a sauropsidan specialization associated with the relatively immense size of the striatum in reptiles and birds. The rich strio-thalamic connections form a thick bundle of fibres which sweep round and encircle the nucleus, delimiting it very sharply from neighbouring elements. It is thus unreasonable to expect that its homologue in the mammalian thalamus will necessarily resemble it in shape and proportions, as the relative development of the striatum is very different. It is necessary to mention this point as attempts have been made to homologize certain elements in the mammalian thalamus with the nucleus rotundus on the basis of relative size and shape. It is in reptiles that the mammillo-thalamic tract (bundle of Vicq d'Azyr) can first be recognized. It can only be defined, however, in certain forms, e.g., *Draco volans* (De Lange [36]). In most reptilian brains the tract is apparently undifferentiated from the diencephalic periventricular system of fibres, of which it was initially a part. The rostral fibres of this system, it would seem, become condensed to form a compact bundle which links up the mammillary region of the hypothalamus with the anterior part of the nucleus dorso-lateralis anterior as well as with a group of more medially situated cells belonging rather to the nuclei of the mid-line (*vide infra*, p. 438). This condensation of periventricular fibres is represented in the diagram (fig. 1 *C*). The anterior part of the dorso-lateral nucleus probably represents the antero-ventral nucleus of the mammalian thalamus. Why it should be the anterior part of the main somatic sensory element of the thalamus which thus becomes especially related to the hypothalamus is not clear, but it may perhaps be conjectured that as the dorsal, lateral, ventral and caudal regions are concerned with the reception of optic, tectal and lemniscal fibres, the rostral region is given over to this special development of the periventricular system.

At the tecto-thalamic junction near the dorsal surface a pretectal nucleus is to be recognized which is in close relation to the optic system and from which efferent tracts descend to the tegmentum of the mid-brain. This nucleus is apparently the equivalent of the pretectal nucleus of mammals which receives lemniscal fibres as well as sensory impulses relayed from the tectum.

In the mammalian thalamus (fig. 1 *D*) the main sensory nucleus is represented by the ventral nucleus or fillet nucleus. It forms the terminal station for the medial, the spinal, and the trigeminal fillets,

and it becomes differentiated from a mass of cells, which also gives rise to the geniculate bodies and the antero-ventral nucleus. All these elements comprise the lower functional levels of the thalamus which are mainly concerned with the reception of sensory impulses directly from the brain-stem and spinal cord, and from the hypothalamus. It is probable that the ventral nucleus represents an element which in the reptilia becomes differentiated to form the nucleus dorso-lateralis anterior and at least a part of the nucleus rotundus. The mammillo-thalamic tract has in mammals become a very well defined bundle which reaches its greatest development in higher mammalian types. In association with this fact the anterior nucleus in which it terminates attains its most complete definition in these forms (so far as its antero-ventral element is concerned). The less specialized part of the peri-ventricular system persists as a more diffuse tract of fibres and intermingled cells linking up the hypothalamus with the mid-line nuclei of the thalamus. The pretectal nucleus is best developed in primitive mammals.

A distinctive feature of the mammalian thalamus is the development of an upper level (topographically and functionally speaking) which is not represented in submammalian forms. This occupies the dorsal part of the thalamus, above the ventral nucleus, from which it is more or less separated by transversely disposed intralaminar nuclei, and comprises such nuclear masses as the lateral nucleus and the dorso-medial nucleus (see fig. 4). These upper levels receive no significant afferent connections from lower sensory centres except by relays through the lower levels of the thalamus. They are related rather to the "association" areas of the cortex, whereas the nuclei of lower thalamic levels are connected with the sensory projection areas, and they exhibit a progressive increase in relative size and elaboration in higher mammalian types culminating in the primates where the association areas of the cortex attain to their fullest development.

General Nuclear Configuration of the Mammalian Thalamus.

In serial sections through the thalamus which have been stained to show the cells it is possible to recognize and define a considerable number of individual cell groupings which may be mapped out by limiting medullary laminæ and by the morphological type of their constituent cells. By reference to sections stained to show the fibres, these groupings may also be recognized and perhaps further subdivided on the basis of their fibre connections. In this way a variable number

of separate thalamic "nuclei" have been recorded by numerous observers. These nuclei are often poorly circumscribed and grade one into the other. It may be argued, indeed, that many of them hardly deserve to be defined as distinct nuclei, and that a difference in cyto-architecture, for instance, does not necessarily indicate any fundamental morphological or functional differentiation. Thus the appearance of the cells and their arrangement may be altered by the passage among them of fibre paths with which they are not directly connected, or by the mechanical pressure of adjacent structures. However, while freely admitting that some of the thalamic nuclei of descriptive anatomy are not necessarily to be regarded as functional units, it is certain that, as a preliminary to a more complete experimental and clinical investigation, an analysis based upon direct anatomical study is essential. Descriptive superfluities may be discarded later on if and when there are found to be such.

Broadly speaking, the thalamic nuclei may be divided into two groups: *principal nuclei* and *intra-laminar nuclei*. The former consist of fairly well defined and clearly differentiated groups of cells which are homogeneous in their morphology, are more or less circumscribed by surrounding medullary laminæ and are concerned predominantly with the reception of circumscribed fibre tracts. Such nuclei are represented for example by the ventral nucleus and its subdivisions which receive the fillet system of fibres, the anterior nucleus in which terminates the well-defined bundle of Vicq d'Azyr, and the geniculate bodies which receive the optic and the auditory tracts. These principal nuclei can usually be recognized without difficulty in the brains of different mammals. Among the principal nuclei and outlining them are fibre tracts which form medullary laminæ. These laminæ are strewn with cells of various types which are often closely packed and usually small and fusiform in shape; they form the intra-laminar nuclei. They are less well defined than the principal nuclei, they are irregular in outline and their fibre connections are usually diffuse. The latter, indeed, are difficult to determine because a large proportion of the fibres in the intralaminar nuclei are merely fibres of passage which are coursing in among the principal nuclei of the thalamus and inter-connecting the latter. There is no doubt that in some cases (e.g., the nucleus para-centralis) the cells of the intralaminar nuclei really comprise the peripheral zones of the adjacent principal nuclei, their appearance having been modified by the fibres which are interwoven with them. In the course of this paper detailed attention will be given to the principal nuclei of the thalamus only.

In fig. 2 a diagram is given representing schematic sections through the anterior, middle and posterior parts of the thalamus of a primitive and generalized mammal. From this diagram the main thalamic nuclei and their relative position may readily be apprehended. In the anterior section, the three elements of the anterior group of nuclei are shown, the antero-dorsal, antero-ventral and antero-medial nuclei. These three nuclei are the terminal station of the fibres of the bundle of Vicq d'Azyr or the mammillo-thalamic tract. The antero-dorsal nuclei are shown connected across the mid-line by a strand of cells

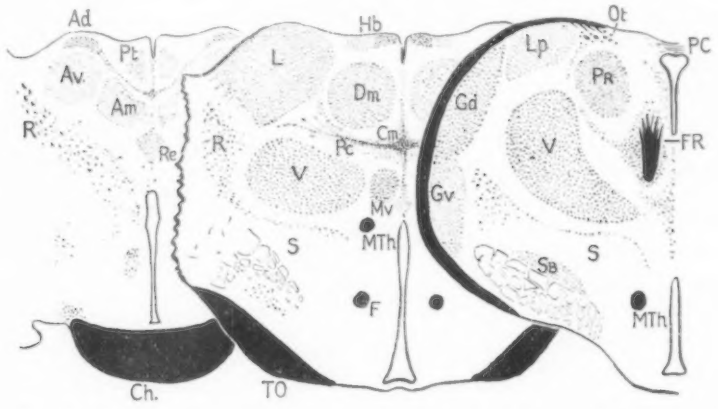

FIG. 2.—Diagram representing sections through the thalamus of a simple and generalized mammalian brain to show the relative position of the principal thalamic nuclei. *Ad.* Antero-dorsal nucleus. *Am.* Antero-medial nucleus. *Av.* Antero-ventral nucleus. *Ch.* Optic chiasma. *Cm.* Nucleus centralis medius. *Dm.* Nucleus dorso-medialis. *F.* Fornix. *FR.* Fasciculus retroflexus. *Gd.* Dorsal nucleus of the lateral geniculate body. *Gv.* Ventral nucleus of the lateral geniculate body. *Hb.* Habenula. *L.* Lateral nucleus. *Lp.* Pars posterior of the lateral nucleus. *MTh.* Mammillo-thalamic tract. *Mv.* Nucleus medialis ventralis. *Ot.* Large-celled nucleus of the optic tract. *Pc.* Nucleus paracentralis. *PC.* Posterior commissure. *Pr.* Pretectal nucleus. *Pt.* Nucleus paratænialis. *R.* Nucleus reticularis. *Re.* Nucleus reuniens. *S.* Sub-thalamus. *Sb.* Nucleus subthalamicus. *TO.* Optic tract. *V.* Ventral nucleus.

which forms an interstitial nucleus of a commissure (commissura inter-antero-dorsalis). Above this commissure and close to the mid-line is the paratænial nucleus. The mid-line nuclei are represented by the paraventricular nucleus and the nucleus reuniens. Ventro-laterally is the nucleus reticularis, consisting of cells scattered among the fibres of the thalamic radiations.

In the next section, through the middle part of the thalamus, the intralaminar nuclei associated with the periventricular system of fibres and with the commissural fibres of the massa intermedia form a cruci-

form arrangement which divides the cross-section of the thalamus into quadrants. Condensations of cells in the median line form a series of mid-line nuclei of which two are shown at this level, the nucleus centralis medius and the nucleus reuniens. The strands of intralaminar cells which extend laterally from the nucleus centralis medius among the commissural fibres form the nucleus paracentralis and the nucleus centralis lateralis, and are continuous rostrally with the commissure between the antero-dorsal nuclei. Below the paracentral and lateral central nuclei is the large ventral nucleus which is the end-station of the fillet system, and which is bounded ventrally by the ventral medullary

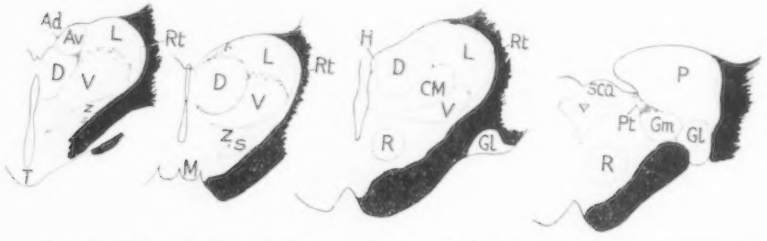

FIG. 3.—Diagram representing sections through the human thalamus to show the relative position of the main thalamic nuclei. *Ad.* Antero-dorsal nucleus. *Av.* Antero-ventral nucleus. *CM.* Centre median nucleus. *D.* Dorso-medial nucleus. *Gl.* Lateral geniculate body. *Gm.* Medial geniculate body. *H.* Habenula. *M.* Mammillary body. *P.* Pulvinar (pars posterior of the lateral nucleus). *Pt.* Pretectal nucleus. *R.* Red nucleus. *Rt.* Nucleus reticularis. *S.* Subthalamic nucleus. *SCQ.* Superior corpus quadrigeminum. *T.* Tuber cinereum. *V.* Ventral nucleus.

lamina and, below this, by the zona incerta of the subthalamus. Close to the mid-line is the rounded nucleus medialis ventralis which further forwards merges with the antero-medial nucleus. The dorsal moiety of the thalamus which is marked off by the transverse intra-laminar nuclei contains the main part of the lateral nucleus and the dorso-medial nucleus. The former is small in primitive brains, but expands considerably in higher forms. The same observation may be made on the dorso-medial nucleus which is bounded laterally by the medial medullary lamina and medially by the paraventricular nucleus of the mid-line group of nuclei. Dorsal to it are seen the medial and lateral habenular nuclei which form a part of the epithalamus.

In the caudal section the fasciculus retroflexus of Meynert or habenulo-peduncular tract is shown descending to the interpeduncular ganglion, and embedded in an intralaminar nucleus, the nucleus para-fascicularis, which is differentiated from the caudal extremity of the paracentral nucleus. The ventral nucleus extends dorso-laterally to the

lateral medullary lamina. The optic tract is shown passing up the side of the thalamus and coming into relation successively with the ventral nucleus of the lateral geniculate body, the dorsal nucleus of the lateral geniculate body, the pars posterior of the lateral nucleus (which is continuous anteriorly with the main part of the lateral nucleus) and the large-celled nucleus of the optic tract. Just caudal to this level, the fibres of the optic tract reach the anterior colliculus of the mid-brain. Subjacent to the large-celled nucleus of the optic tract is the pretectal nucleus which lies at the tecto-thalamic junction, and is situated immediately behind the upper end of the fasciculus retroflexus. At a more caudal level the medial geniculate body replaces the lateral geniculate body. The relative position and size of the principal thalamic nuclei in the human brain are indicated in fig. 3.

For purposes of description, the principal thalamic nuclei may be grouped as follows:—

A.—*Lower levels of the thalamus.*

(1) Ventral group of nuclei, including the main ventral nucleus of the thalamus and its subdivisions, and the nucleus medialis ventralis.

(2) Anterior group of nuclei.

(3) Nuclei related to the optic tract, including the dorsal and ventral nuclei of the lateral geniculate body, the large-celled nucleus of the optic tract, and the pretectal nucleus.

(4) Medial geniculate body.

B.—*Upper levels of the thalamus.*

(1) Lateral group of nuclei, including the pars principalis, or main part of the lateral nucleus and its subdivisions, the pars posterior of the lateral nucleus, and the nucleus supra-geniculatus.

(2) The centre median nucleus.

(3) The dorso-medial nucleus.

The diagrams reproduced in this paper are purely schematic.

The Ventral Group of Nuclei.

The ventral nucleus of the thalamus and the lemniscus system.—The dorsal part of the diencephalon may be regarded as a terminal sensory correlation centre where afferent somatic impulses are brought into functional relation with each other and through hypothalamic connections with impulses from olfactory and visceral centres. In primitive forms these sensory impulses are for the most part relayed from the tectum of the mid-brain and are carried almost entirely by the tecto-

thalamic connections, though even in the simplest brain (e.g., petromyzon and teleostean fishes) there exist more direct paths to the thalamus from lower levels which do not relay in the mid-brain. In simple mammalian brains these tracts become much more predominant and are represented by the spino-thalamic tracts from the dorsal horn cells of the spinal cord, the medial lemniscus from the terminal nuclei of the posterior columns of the spinal cord, the trigeminal lemniscus from the sensory nucleus of the fifth cranial nerve, the lateral lemniscus from the auditory nuclei in the medulla and the optic tract fibres. The fibres of these sensory tracts terminate in nuclear groups which are primitively parts of a homogeneous collection of cells forming part of the pars dorsalis diencephali. The termination of the optic and auditory tracts in the lateral and caudal regions of this common sensory centre leads to a local differentiation of the dorsal nucleus of the lateral geniculate body and the main part of the medial geniculate body respectively. From the greater part of the centre, which receives impulses of general sensation, the ventral nucleus of the thalamus and its subdivisions become progressively developed. In a mammalian brain of primitive type (e.g. the brain of a generalized insectivore) there is little intrinsic differentiation of the ventral nucleus; it is represented by a uniform collection of moderately large nerve-cells which form a group of a roughly spherical shape occupying approximately the centre of the diencephalon. This is the "noyau sensitif" of Cajal [5]. It is bounded in front by the reticular nucleus, the anterior nuclei, and the mammillo-thalamic tract, the latter curving up round its anterior convex surface. Behind it is limited by the fasciculus retroflexus and the nucleus parafascicularis. Dorsally, the ventral nucleus is separated by medullary laminæ and intralaminar nuclei, such as the n. paracentralis and the n. centralis lateralis, from the dorsomedial nucleus, the lateral nucleus and the pulvinar, and below it rests on the subthalamus from which it is separated by the ventral medullary lamina. Medially it is related to the nuclei of the mid-line and laterally the lateral medullary lamina serves to mark it off from the lateral geniculate body and the pulvinar (see figs. 2, 3, 9 and 10).

In its simple undifferentiated form, the ventral nucleus is easy to define by its cytoarchitecture as well as by the medullary laminæ which surround it. The terminal fibres of the fillet system sweep round the nucleus on all sides, though mainly from the ventro-lateral aspect, and, penetrating it, form a rich plexus of medullated fibres which tends to separate up constituent cells into clusters and to give to the whole

nucleus a characteristic lobulated appearance. In some cases the separation of the antero-ventral nucleus from the ventral nucleus is not very clear. In a form such as Erinaceus (the hedgehog), in which the optic tracts are small, the boundary between the dorsal nucleus of the lateral geniculate body and the ventral nucleus is poorly defined, and in the minute brain of the common shrew (Sorex) the ventral nucleus is continued caudally without interruption into the medial geniculate body. In higher mammals these structures are much more differentiated, but here there may be difficulty in defining the precise boundary between the dorsolateral portion of the ventral nucleus and the lateral nucleus. The rich fibre connections which develop between the ventral and lateral nuclei as they undergo progressive differentiation tend to break up the outlines of these two nuclear masses where they are contiguous with each other.

In larger mammals the tendency to "lobulation" of the ventral nucleus is expressed by the more complete splitting up of the nucleus into several elements which may be distinguished from each other with a varying degree of clearness by reference to intervening medullary laminæ as well as by the character of their constituent cells. Thus Rioch [52], in carnivores, recognizes five subdivisions of the ventral nucleus, and in higher primates (lemur [47], cercopithecus [19], and man) a similar but still more complicated type of differentiation exists. The functional significance of these subdivisions is not yet known and, indeed, it is hardly profitable to attempt an investigation into this problem until their topography and homologies have been defined with more exactitude. The presumption is that each element is related to particular groups of fibres in the medial fillet, and if there is a definite spatial localization of fibres in the fillet according to their source of origin there is probably a localization of the same order in the ventral nucleus.

The shape of the ventral nucleus is influenced and modified by the development of adjacent nuclear masses. Thus in higher mammals the greater relative size of the dorsal nuclei of the thalamus, and especially the centre median nucleus, leads to a compression and flattening of its medial part and the nucleus expands considerably in a lateral direction. The ventral nucleus forms the main terminal station for the lemniscus system of fibres. These approach it mainly from the ventral aspect where they form a great part of the ventral medullary lamina, and, as Cajal has described, they enter the nucleus and break up into complicated terminal arborizations among its constituent cells. The main efferent

connections in mammals, on the other hand, are with the neopallium by way of abundant thalamo-cortical radiations. The ventral nucleus thus comes to form an important relay station through which somatic impulses are projected on to the cerebral cortex and it must therefore play a significant rôle in association with the evolutionary development and differentiation of the cortex. It is thus a matter of considerable interest to study the precise mode of termination of the lemniscus fibres and to note whether they end also in relation to thalamic nuclei other than the ventral nucleus. As we shall see, there is some uncertainty on these points and much of the evidence available is open to criticism, partly because of the confusion in terminology.

Wallenberg [60] investigated the destination of the fillet in rabbits. He found that fibres from the nucleus gracilis end in the ventromedial part of the ventral nucleus (as well as in the substantia nigra, zona incerta and hypothalamus), while those from the cuneate nucleus end in its middle and lateral parts. The trigeminal lemniscus from the spinal nucleus of the fifth nerve passes up in a dorsal position into the internal medullary lamina of the thalamus to reach the dorso-lateral angle of the ventral nucleus and the ventrolateral angle of the "medial nucleus." Unfortunately, it is not quite clear what Wallenberg understood by the "medial" nucleus, or whether he found evidence of degeneration of terminal fibres within the substance of this nucleus. In the rabbit only sensory tracts, the fibres of which spring from the most frontal part of the spinal cord and from the brain-stem, reach the thalamus; the secondary spinal paths mainly end in the hind- and mid-brain. From his figures [60] it seems that the "medial" nucleus to which he refers is the pretectal nucleus (prebigeminal or posterior nucleus of other authors), for it clearly lies caudal to the upper end of the fasciculus retroflexus, and it has been established by numerous observers that fillet fibres terminate here. His comparison of the relative size of this nucleus in the mouse and rabbit (which he compares to the relative size of the trigeminal fillet in these animals) also refers to the pretectal nucleus. My own studies certainly show no correspondence between the development of the trigeminal system and the dorso-medial nucleus (Monakow's nucleus medialis *a*) in different animals. It might be expected that a study of the brain of Ornithorhynchus would be of great interest in this respect. The normal thalamus of this monotreme has been studied in some detail by Marion Hines [28], but its structure seems to be so aberrant in many respects that it is not easy to be certain of homologies. Hines identifies a

"medial" nucleus which she states is connected with the striatum and the secondary medial olfactory centres; caudally it is continuous with a nucleus ventrolateralis, the rostral portion of which receives fibres of the trigeminal lemniscus while the posterior part is the termination of the medial lemniscus. It is improbable that any of these elements corresponds to the dorso-medial nucleus of the mammalian thalamus. On the other hand there is no doubt that the "n. ventrolateralis" of the monotreme thalamus is the equivalent of the mammalian ventral nucleus. In Ornithorhynchus, in which the trigeminal system is prodigiously developed, there is an astonishing hypertrophy of the ventral nuclear element, and it can hardly be doubted that these two features are interrelated. Moreover, if the dorso-medial nucleus is to be identified at all in this brain, it certainly is no larger relatively than in other mammalian brains of an average normal structure. Here, then, is additional evidence that the trigeminal filiet is terminally related to the ventral nucleus and not to the dorso-medial nucleus.

Perhaps the most extensive work on the ascending thalamic tracts is that of Probst [50], who collected serial sections of forty experiments in which the lemniscus was cut and was thus able to study the resulting degeneration in great detail. Probst found that the fibres from the gracile and cuneate nuclei end in the nucleus ventralis *a* (employing von Monakow's nomenclature). He followed a few across the posterior commissure into the caudal and medial part of the thalamus of the opposite side, but this latter observation is considered by other observers (e.g., Wallenberg) uncertain, since osmic granules are so frequently to be observed in the posterior commissure in normal material stained by the Marchi method. After lesions of the anterior funiculus of the spinal cord in the cervical region, Probst traced degenerated fibres through the lateral part of the medial fillet which ended in the ventral nucleus *a* of the same side as the lesion. These evidently represent the ventral spinothalamic tract. The fibres of the trigeminal lemniscus from the substantia gelatinosa were followed across the mid-line as fibræ arcuatæ into the most medial part of the medial fillet and thence into nucleus ventralis *a* and nucleus ventralis *b*, and also into the most caudal part of n. medialis *b* and n. medialis *c*. The two latter nuclei represent intralaminar nuclei, and Probst did not describe any fibres of the lemniscus system as terminating in the dorso-medial nucleus (von Monakow's nucleus medialis *a*).

Vogt [58] produced an experimental lesion in the nucleus cuneatus of a cercopithèque monkey and followed the degenerated fibres up in

the medial fillet. In the text it is stated that degeneration was noted throughout the medial fillet, though the accompanying figures indicate that it predominated in the lateral fibres. Most of the degenerated fibres terminated in a part of the ventral nucleus called the caudal ventral nucleus, or *v.a.*, and none were traced into the lateral nucleus or into the "noyau ventral intermédiaire." The author stresses the sharp line of demarcation between the ventral and lateral nuclei of the thalamus in regard to the distribution of degeneration granules. Some degenerated fibres also penetrated the "noyau semilunaire," or *v.b.* (another element of the ventral nuclear group), and a few were found in the capsule and in the substance of the centre median nucleus. This suggestion that some of the medial fillet fibres end in the centre median nucleus is also made by Dejerine, but it is a matter which requires further investigation (*vide infra*, p. 463). The plates which accompany Vogt's paper are not convincing on this point, and absence of terminal degenerated fibres in the centre median nucleus (or its equivalent in lower mammals) after a lesion involving the medial fillet, seems to be the general rule, as it was certainly in my own experiments [12]. There is evidence that the caudo-ventral part of the centre median nucleus is traversed by fibres of passage of the medial fillet to the medio-dorsal region of the ventral nucleus, and it seems probable that the degeneration found by Vogt represents these fibres. If any fillet fibres really terminate in the centre median nucleus, they must be extremely few and of minimal significance. Certainly there is no evidence, as far as I know, of trigeminal fibres terminating here, in spite of the statements to this effect in many modern textbooks. Vogt himself believes that trigeminal fibres reach the intermediate part of the ventral nucleus.

Cajal [5] has described the termination of the main fillet in the main part of the ventral nucleus, his *noyau sensitif*, but collaterals also end in relation to the pretectal nucleus. He further states that trigeminal lemniscus fibres send collaterals to the anterior and posterior semilunar nuclei and terminate in the zona incerta of the subthalamus. It is not quite clear what are the homologies of Cajal's semilunar nuclei; it seems probable, however, that they represent merely the anteroventral and posterodorsal marginal zones of the main ventral nucleus (and in the latter probably also the intralaminar group of paracentral and lateral central nuclei) where the rich permeation of ascending fibres leads to a local differentiation. If so, the trigeminal fibres end in the peripheral parts of the ventral nucleus. Cajal does not indicate that any of these fibres end in connection with the dorso-medial nucleus (his intermediate dorsal nucleus).

Huber and Crosby [31] believe that in the medial lemniscus, from the lateral to the medial border, are situated successively lateral spinothalamic, gustatory and proprioceptive fibres, and that, in their termination in the thalamus, these groups of fibres are distributed in the same order to different parts of the ventral nucleus in a latero-medial direction. This suggestion, however, still requires to be tested experimentally.

Papez [44], in a short note, describes the termination of the medial fillet after section of the tract in the tegmental region. The main site of termination is stated to be the "ventral and lateral nucleus." It is not possible to infer from this whether the lateral nucleus referred to is anything more than the lateral part of the ventral nucleus. A doubtful few of the fillet fibres were traced into the substantia nigra and the posterior commissure, but none were found to end in the zona incerta. Other fibres were followed to the posterior nucleus of the thalamus (= pretectal nucleus) along the course of the numerous thalamo-cortical fibres in this region.

Allen (1) describes in the guinea-pig the caudal part of the lateral region of the ventral nucleus (von Monakow's nucleus ventralis *a*) as the terminal for most of the medial lemniscus fibres, but he also describes some as ending in the caudal pole of the lateral nucleus. From a study of his figures, however, it seems that this lateral nucleus represents the dorsomedial part of the posterior ventral nucleus of Gurdjian's classical description. It may further be noted that Allen states that very few, if any, of the medial lemniscus fibres are distributed to the red nucleus, regio subthalamica or formatio reticularis. Rioch [54], from a study of normal material only, reports that in carnivores fibres from the medial division of the medial fillet enter the caudal pole of the lateral group of thalamic nuclei, but he was unable to follow these to their termination. There is, indeed, no certain evidence that any fibres of the fillet system end in those thalamic elements which—on the basis of recent descriptive anatomical work—come under the designation of lateral nucleus, and there is abundant negative evidence that they do not do so. In my own observations by Marchi's method, following lesions of the medial and trigeminal fillets in the rat [12], terminal degeneration in the thalamus was limited to the ventral nucleus (and the pretectal nucleus). Some of the degenerated fibres ran forward in the medial medullary lamina in the region of the paracentral and lateral central nuclei to the dorsal part of the ventral nucleus.

A critical survey of the observations of various authorities on the

mode of termination of the fillet in the thalamus shows complete unanimity in regarding the ventral nucleus as the main terminal nucleus of these sensory fibres. It is particularly to be noticed that many of these fibres sweep round the dorsal and ventral surfaces of the rounded ventral nucleus before penetrating it, and they thus course through intralaminar nuclei on their way. In Probst's account, nucleus ventralis *a* and nucleus ventralis *b* represent parts of the main ventral nucleus of the mammalian thalamus (corresponding probably to the pars arcuata and pars medialis of the ventral nucleus in the dog and cat according to Rioch). It is not easy to assess the evidence for the statement frequently made that part of the lemniscus system—and especially trigeminal fibres—end in the "medial nucleus." It seems that as a result of the looseness of nuclear terminology the results of experimental work have been persistently misrepresented by many authors. Thus Probst in his detailed investigation only claims to have found degenerated fibres after section of the fillet in n. medialis *b* and n. medialis *c*. These nuclei of von Monakow's terminology are the equivalent of n. paracentralis and n. centralis lateralis (Rioch). In other words they represent merely intralaminar nuclei in the medullary lamina which forms part of the capsule of the main ventral nucleus, separating the latter from the nuclei of the dorsal part of the thalamus, e.g., the lateral and dorso-medial nuclei. It seems probable that these degenerated fibres are components of the fillet which are sweeping round the ventral nucleus to reach its dorsal and rostral part. Unfortunately, the term "medial nucleus" has usually been applied in human descriptive anatomy to what is here called the dorso-medial nucleus, and the assumption has thus arisen that the latter is the site of termination of lemniscus fibres. So far as I am aware, however, no definite evidence has ever been adduced to indicate that—whatever may be the case with other nuclei sometimes included in the medial group—the dorso-medial nucleus receives such terminals. If fillet fibres actually terminate in connection with the cells of the intralaminar nuclei (n. medialis *b* and *c* of von Monakow) this need not qualify the statement that the ventral nucleus is the fillet nucleus (noyau sensitif), since these intralaminar nuclei largely consist of the peripherally situated cells of the ventral nucleus which are modified in appearance by their close relation with the interwoven fibres of the medullary lamina.

Relation of lemniscus system to the ventral part of the diencephalon.—In addition to the main termination of the medial fillet in the dorsal part of the diencephalon, there is evidence that some of

its fibres end in the subthalamus and hypothalamus. Thus Wallenburg traced fibres from the nucleus gracilis to the substantia nigra, zona incerta and mammillary body. The termination in the substantia nigra is accepted by several authorities (e.g., Elliot Smith [17], Winkler [63]), but the connections with the zona incerta and mammillary body are less certain. It is suggested that fillet fibres reach the latter by way of the peduncle of the mammillary body. It is probable that this peduncle consists, at any rate mainly, of ascending fibres (Wallenberg [59], Edinger [15], Cajal [5], Papez [44], Allen [1], &c.), and it is thought by some that these fibres are derived from the medial lemniscus and probably carry gustatory impulses. This problem remains yet to be settled, but it may be noted that Herrick has demonstrated the existence of anatomical connections between gustatory nuclei and the hypothalamus in the primitive brains of teleostean fishes, and it is not unlikely that this ancient pathway still exists in higher forms. Such a connection would fall into line with the clinical observation that disturbances of gustatory sensations are associated with lesions of the uncus of the temporal lobe, for the mamillary body is related directly to the uncus by way of the fornix system. Kappers [35] suggests that fillet fibres in the mammillary peduncle represent the spino- and bulbo-hypothalamic paths described in sub-mammalian forms.

Intrathalamic connections.—In a paper dealing with the lateral geniculate body [11] I noted the intimate fibre connection between the dorsal nucleus of this structure and the ventral nucleus, forming in primitive brains of mammals in which the visual apparatns is well developed (e.g., Macroscelides, Pteropus and Tupaia) a conspicuous and compact bundle. A similar connection between the ventral nucleus and the medial geniculate body has been studied with the degeneration method by Glorieux [22]. This author describes in the dog a fasciculus metathalamo-thalamo-corticalis which runs forwards from the medial aspect of the medial geniculate body and to a large extent terminates in the whole extent of the ventral nucleus. Rioch [54] has studied the intrathalamic connections of the ventral nucleus in normal carnivore and gives the following results: The pars anterior is mainly connected with the other elements of the ventral nucleus and has very few connections with the lateral, medial and anterior nuclear groups. The pars medialis is connected with the n. submedius (n. medio-ventralis), dorso-medial nucleus, n. lateralis and the periventricular system of fibres. The pars arcuata is connected with the n. submedius, n. lateralis, medial geni-

culate body, anterior and posterior colliculi, and the pars externa with the hypothalamus and subthalamus, including the zona incerta. In addition there is a free communication across the commissura mollis with the ventral nucleus of the opposite side. My own comparative studies indicate that the main intrathalamic connections of the ventral nucleus are: (1) With other nuclei of its own functional level, i.e., the medial and lateral geniculate bodies; (2) with the main part of the lateral nucleus, which in this respect bears the same relation to the main ventral nucleus that the pulvinar or pars posterior of the lateral nucleus does to the lateral geniculate body; and (3) with the periventricular system of fibres by which it is especially brought into functional relation with the hypothalamus and subthalamus. The connections with the dorso-medial nucleus seem to me to be relatively insignificant.

Connections with lower levels.—The fillet system has already been discussed. There are numerous tectal connections with the ventral nucleus, especially with its caudal third, probably conducting in both directions. These run largely in the lateral medullary lamina of the thalamus and are much more evident in the brains of primitive forms. In lowly vertebrates, indeed, most of the sensory impulses which are destined to reach the *anlage* of the mammalian ventral nucleus are relayed through the tectum by tecto-thalamic fibres.

A significant proportion of the fibres of the brachium conjunctivum, which emerge from the dentate nucleus of the cerebellum, terminate in the ventral nucleus, having passed up on the medial aspect of the red nucleus. This relation has been studied exhaustively in the guinea-pig by Allen, who found that in this rodent the cephalic end of the large lateral nucleus ventralis thalami (nucleus ventralis *a*) is the terminus for most of the thalamic fibres of the brachium conjunctivum. The only other element of the dorsal part of the diencephalon to which he could trace any of these fibres was a "medial nucleus" which, judging from his figures, probably is the equivalent of the nucleus parafascicularis. In the human brain, Probst describes fibres of the superior brachium ending in the more medial of the ventral nuclear group of the thalamus.

It may be relevant to note here that Sachs [55] records a descending degeneration in the posterior longitudinal bundle after a lesion involving the ventral nucleus, and he traced collaterals from these fibres to the nuclei of the fifth, sixth, eighth and tenth cranial nerves. These observations, however, have not been confirmed, and there is negative evidence against their acceptance.

Cortical connections of the ventral nucleus.—The rich connections between the ventral nucleus and the internal capsule by way of the thalamic radiations are very conspicuous in Weigert preparations of this region. There is reason to believe that the great proportion of these fibres extends to the cortex, but it is generally believed that at least some of them terminate in the caudate nucleus and putamen, forming a part of the thalamo-striate system. The precise relation of different parts of the ventral nucleus to various cortical areas is a question of considerable importance, but in spite of the work which has been done by numbers of investigators on this problem there still remains much uncertainty about it. This is mainly due to the great technical difficulties in approaching the problem experimentally. Many years ago von Monakow [43] studied the thalamo-cortical connections by the method of van Gudden, i.e., by removing portions of the cortex in young animals and searching for the atrophic changes which occurred in the thalamus after a considerable interval of time. It is generally conceded, however, that this method is unable to provide accurate results in a question of this kind. It has been recognized from the time of von Monakow and Cajal that the different parts of the thalamus are projected on to areas of the cortex which occupy relatively similar positions. Thus, fibres from the anterior part pass towards the frontal lobe, those from the posterior part towards the occipital lobe, and so on. Elliot Smith [16] has shown how this conception can be held to explain to a considerable extent the known distribution of cortical areas.

As the result of scattered observations on clinical cases, it is generally held that the ventral nucleus in man is mainly related by corticipetal fibres with the pre- and post-central gyri and with neighbouring parts of the frontal and parietal lobes, but more especially with the somæsthetic projection areas. The cortical radiations of the ventral nucleus in lower mammals, however, are probably more diffusely distributed over the neopallium in correlation with the less definite differentiation of the cortical fields and with their relative functional equipotentiality. There are scattered experimental observations dealing with this point and also an extensive report by Minkowski [42] on cortical connections in the monkey which gives a good deal of apposite information. Probst records that in the cat a lesion in the caudo-ventral nucleus leads to a degeneration which is distributed mainly to the coronary gyrus. Sachs [55], in the monkey, notes that thalamo-cortical fibres from the "ventral region of the lateral nucleus" (presumably equivalent to the ventral nucleus of most authors) are distributed only to the motor area

and the post-central gyrus. Minkowski states that in the monkey fibres run from the anterior part of n. ventralis *a* (n. ventralis lateralis of von Monakow) and the adjacent part of the n. ventralis anterior to the middle part of the ascending frontal gyrus (the arm area), and from the anterior part of n. ventralis *b* (n. ventralis medialis) to the opercular region of the ascending frontal convolution. Fibres pass from the middle part (in the anterior-posterior sense) of n. ventralis *a* to the middle segment of the area (arm area) and from the lateral part of the posterior segment of n. ventralis *b* to the post-Rolandic opercular region. For the parietal area (comprising cortical fields 5 and 7 of Brodmann) fibres pass from the posterior extremity of n. ventralis *a* and n. ventralis *b* to the supramarginal gyrus, and from n. ventralis *c* to the posterior extremity of the supramarginal gyrus. Lastly, corticipetal fibres are described as connecting the anterior extremity of the n. ventralis anterior to (probably) the postero-inferior part of the frontal region.

In regard to cortico-thalamic connections of the ventral nucleus, the available evidence is more complete. Riese [51], in dogs, traced corticifugal fibres from the area precentralis to the ventral nucleus, especially n. ventralis *a*. In a cat, he found that lesions of the frontal lobes produced a fine degeneration in nucleus ventralis *c*. Biemond [2], in the rabbit, followed degenerated fibres into the caudal part of the ventral nucleus after cortical injuries, of which one involved fields 17 and 29, another the frontal lobes, and a third fields 29, 7, 17 and 18. In all these cases the degeneration in the ventral nucleus was slight. In monkeys, however, Biemond traced no corticothalamic fibres into ventral nucleus, and herein he is in complete agreement with Minkowski's experimental observations on the same animal. Poljak [48], in his observations on the degeneration following cortical lesions in the cat, does not specify the precise regions of the thalamus in which he found degenerating corticothalamic fibres. However, his figures indicate that in two of his cases, with injuries to the cortex of the parietal area (suprasylvian convolution), and of the insular areas, degenerated fibres penetrated into the ventral nucleus.

My own observations on the degeneration resulting from circumscribed lesions in different parts of the cortex in the rat's brain indicate that in this animal almost every part of the neopallium is connected by corticifugal fibres with the ventral nucleus except the anterior pole of the frontal lobe, the cingular areas, the striate area and probably the caudal margin of the temporal lobe. The latter two cortical areas are related to other thalamic nuclei of an equivalent functional level, i.e., the

lateral and medial geniculate bodies. Moreover, I found that these cortico-thalamic fibres terminate in regions of the ventral nucleus which correspond in their relative positions to the topography of the cortical area involved.

From a consideration of these results, it would appear that the corticothalamic connections of the ventral nucleus are much more abundant in the brains of primitive mammals, and that in the advanced types (e.g., primates) they are absent altogether. This is a point that requires careful consideration in connection with the theories of sensation which postulate a reciprocal fibre connection between the cortex and the ventral nucleus as the underlying anatomical basis of the cortical inhibition of thalamic activities.

The evolutionary differentiation of the ventral nucleus.—It has already been pointed out that the ventral nucleus of the mammalian thalamus is represented in lowly vertebrates (fishes and amphibia) by an undifferentiated and diffuse mass of cells in the pars dorsalis diencephali which Herrick has called the pars dorsalis thalami. This he showed (in amphibia) to be the great receptive centre of the diencephalon for somatic afferent impulses. The posterior part of this mass receives the spinal and lateral lemnisci, the middle and largest part receives tecto-thalamic fibres and possibly hypothalamic fibres representing the bundle of Vicq d'Azyr, while the dorsal part is the terminal for optic fibres. It is evident that the dorsal and caudal regions of this mass represent the *anlagen* of the geniculate bodies, while from the intermediate parts is differentiated the main ventral nucleus of the thalamus as well as other elements, such as a portion at least of the anterior nucleus.

In reptiles and birds the thalamus shows more nuclear differentiation. One of the most conspicuous nuclei in these vertebrates is the nucleus rotundus, a spherical mass of large cells which is usually well defined by a capsule of fibres and which occupies approximately the central region of the dorsal part of the diencephalon. In different species the nucleus rotundus merges to a greater or lesser extent with the nucleus dorsolateralis anterior, a nucleus which is more diffuse but which contains the same type of cells. Both these nuclei are related by fibre connections with the lateral areas of the fore-brain and thus belong to what has been called the "somatic thalamus." As regards the nucleus rotundus we believe (with Ingvar [33], Crosby [31] and others) that the homologue of this characteristically sauropsidan nucleus is to be found in the ventral group of nuclei of the mammalian thalamus. It seems also probable that at least a part of the n. dorsolateralis anterior

(i.e., excluding that portion which is related to the mammillothalamic tract and therefore to be regarded as representing one of the elements of the anterior nucleus) is represented in the ventral nucleus.

The topographical position of the nuclear rotundus in relation to the mamillo-thalamic tract, the main part of the habenulo-peduncular tract, the subthalamus, and other elements, is suggestive of its homology with the ventral group of nuclei. The general similarity in appearance of these nuclei in sagittal sections is quite striking if the thalamus of a primitive mammal (e.g., Erinaceus, Notoryctes, Sorex) is compared with that of a reptile such as *Draco volans*, as figured by De Lange in his monograph.

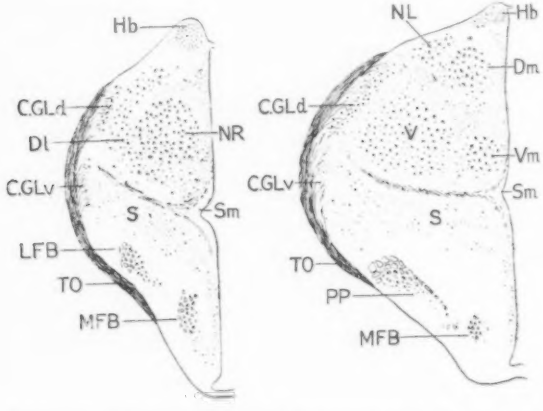

FIG. 4.—Schematic sections through the diencephalon of *A*, Reptile, and *B*, Mammal, illustrating the homologies of certain thalamic elements. *CGLd*. Dorsal nucleus of the lateral geniculate body. *CGLv*. Ventral nucleus of the lateral geniculate body. *Dl*. Nucleus dorso-lateralis anterior. *Dm*. Nucleus dorso-medialis. *Hb*. Nucleus habenulæ. *LFB*. Lateral forebrain bundle. *MFB*. Medial forebrain bundle. *NL*. Nucleus lateralis. *NR*. Nucleus rotundus. *PP*. Pes pedunculi. *S*. Subthalamus. *Sm*. Sulcus medius. *TO*. Optic tract. *V*. Nucleus ventralis. *Vm*. Nucleus medialis ventralis.

The relation of the commencement of the fibres of the habenulo-penduncular tract to the caudal extremity of the nucleus rotundus (passing laterally to it) has been used as an argument against this suggested homology, but it is not possible to rely on such a point, for the dorso-medial nucleus of mammals is not present in the reptilian thalamus and the origin of the habenulo-pedunclear tract is thus brought into immediate relation with the homologue of the ventral nucleus, bearing much the same relation to the latter that it does to the

dorso-medial nucleus in mammals. The fibre connections of the nucleus rotundus favour its homologies with at least a part of the pars dorsalis thalami of amphibia on the one hand, and with at least a part of the mammalian ventral nuclear group on the other. Connecting it with the lateral somatic areas of the fore-brain in sauropsida (i.e., with the neostriatal regions) are abundant thalamo-striatal and strio-thalamic connections which are clearly the precursors of the internal capsule of mammalian brains. The question of cortical connections of the reptilian and avian thalamus has yet to be clearly decided, but if these are absent this does not necessarily invalidate the interpretation that the nucleus rotundus is strictly equivalent to a part of the ventral group of nuclei. It is to be presumed, indeed, that the development of a neopallial cortex must have been preceded by the differentiation of a ventral nucleus from which thalamo-cortical fibres were subsequently projected.

As regards ascending tracts De Lange [36] traced quinto-thalamic fibres in reptiles to the nucleus rotundus, and Huber and Crosby [30] regard it as probable (though they were unable to demonstrate it with certainty) that fibres of the spinal lemniscus and the trigeminal lemniscus terminate in the nucleus. The most conclusive evidence is that of Wallenberg [61] who by Marchi's method in birds followed ascending fibres from the nuclei of the posterior funiculi into the nucleus rotundus. This tractus bulbo-thalamicus is evidently the homologue of the medial fillet. He also found, associated with this bundle, fibres which terminated in the hypothalamus.[1]

The relation of the nucleus rotundus to the lemniscus systems seems to settle beyond doubt its homologies with some part of the ventral group of nuclei of the mammalian thalamus. The suggestion that part of the nucleus dorso-lateralis anterior of the sauropsidan diencephalon is also to be regarded as the precursor of a part of the ventral nucleus is open to dispute on the ground that no direct lemniscus fibres have been traced to it. However, it is evidently very closely related to the nucleus rotundus both topographically and structurally; it is, like the latter, connected with the tectum by tecto-thalamic fibres and with the somatic areas of the fore-brain by the lateral fore-brain bundle, and its lateral portion in some reptilian forms undergoes differentiation as a terminal station for optic fibres in precisely the same way that the dorsal nucleus

[1] It is interesting that Wallenberg also recognized a quinto-frontal tract of fibres in birds which apparently conveys general sensory impulses right up to the neostriatum without interruption in the diencephalon. This tract appears to be an avian specialization.

of the lateral geniculate body appears in primitive mammals to be a delaminated portion of the lateral part of the ventral nucleus [11]. If it is remembered that in the evolution of the sensory paths of the central nervous system tecto-thalamic paths clearly precede the establishment of direct lemniscal connections, these points are all consistent with the interpretation advanced here.

The intrinsic differentiation of the ventral nucleus in the mammalian series has already been referred to above. Until we know more certainly the precise afferent and efferent connections of its various subdivisions it is useless to attempt further discussion on the significance of this differentiation. Presumably it is related to a regional localization comparable with that which is known to exist in the sensori-motor areas of the cortex with which it is so intimately connected. It is also possible that the differentiation may have a functional significance in relation to the different elements of sensation which pour into the thalamus, for it is known from the clinical observations of Head and Holmes [24] that on their approach to the thalamus sensory tracts become progressively segregated in accordance with the nature of the sensory impulses which they carry.

The differentiation of the ventral nucleus into component nuclear groups does not imply a lack of functional unity in the nucleus as a whole. The subdivisions are intimately linked up by intrinsic fibre connections and no doubt are mutually interdependent to a considerable degree. In this question, an observation of Minkowski [42] is particularly apposite. He noted that in cases of partial degeneration of the external thalamic nucleus of Burdach (which includes the ventral nucleus), following ablation of the ascending frontal or ascending parietal convolutions, some parts of the nucleus, although not degenerated, presented an atrophy (general diminution in volume, slight reduction in cell-volume, and reduction of intercellular substance). He believes that an alteration of this kind is to be explained by a certain degree of functional inactivity which is brought about in the whole of the external nucleus as the result of the degeneration of one of its component parts, and that the whole nucleus therefore represents an anatomical and functional unity.

Von Monakow and his workers have maintained that the ventral nucleus of the thalamus is connected only with the arm areas of the cortex, the lateral nucleus being associated with the leg areas. This seems, however, most unlikely to be the case (*vide infra*, p. 456).

Nucleus Medialis Ventralis.

In the thalamus of lower mammals a distinct nuclear element lies close to the mid-line, ventral to the paracentral nucleus, medial to the ventral thalamic nucleus, and extending from the antero-medial nucleus anteriorly to the level of the fasciculus retroflexus behind. This is the nucleus medialis ventralis. It is actually in continuity rostrally with the antero-medial nucleus, so that in some forms at least (e.g., Tarsius [7]), it is not possible to distinguish between them on the basis of cyto-architecture. Whereas in lower mammals the nucleus is rounded and well circumscribed except anteriorly, in the higher primates it becomes more diffuse and is probably included under the heading of the nucleus submedius in some forms, while in others it is not recognizable as a separate unit. A survey of a comparative series indicates, indeed, that the nucleus medialis ventralis becomes progressively smaller and less distinct in the more advanced types. A study of normal Weigert preparations shows that the nucleus is connected by short fibres with the adjacent part of the ventral thalamic nucleus, with the medial medullary lamina, and with the periventricular system (Rioch [54]). In my own experiments on rats, I have not been able to trace any afferent fibres to the nucleus either as the result of cortical, thalamic or tectal lesions, nor have I found any evidence of Marchi degeneration in the nucleus after lesions involving the lemniscal system. In two cases in which lesions were localized in the nucleus medialis ventralis of one side, degenerated fibres were traced in abundance from the site of the lesion through the fasciculi of the internal capsule to the lenticular nucleus, but not extending further to the cortex. It would seem, therefore, that the nucleus is predominantly connected with the striatum. In this connection it may be noted that if there is any one thalamic element in the mammalian brain which can be homologized with the nucleus rotundus of the sauropsidan brain, it is the nucleus medialis ventralis. It satisfies topographical criteria in its relation to other diencephalic elements (bearing in mind that the dorso-medial and lateral nuclei of the mammalian thalamus are not represented as definite elements in lower vertebrates), and its striatal connections compare with the similar connections of the nucleus rotundus. Moreover, it is relatively better developed in primitive mammalian types, and in some (e.g., Pteropus, fig. 10, *Mv*) it is even enclosed by a well-defined capsule of medullary fibres in a manner which recalls the appearance in cross-section of the nucleus rotundus. This homology is suggested tentatively in the diagram shown in fig. 4.

The Anterior Group of Nuclei.

This group is represented typically by three elements in the antero-dorsal part of the thalamus, all of which are characterized by the fact that they are terminal nuclei of the mammillo-thalamic tract (bundle of Vicq d'Azyr). These are termed the antero-dorsal, the antero-ventral, and antero-medial nuclei. They vary in their relative development in different mammals. This variation has been dealt with in a previous communication where also reference was made to their phylogenetic history [9]. The antero-medial nucleus is to be regarded as a part of the "palæothalamus," differentiated from the mid-line nuclei, and apparently having no connection with the cortex cerebri. It is proportionately larger in primitive mammals and is probably the equivalent of the nucleus dorso-medialis anterior of reptiles. In higher mammals (e.g., primates) its identification is doubtful. It is almost certain that what has been called the nucleus antero-medialis in some higher mammals (nucleus anterior *b* of certain authors) is really a differentiated part of the antero-ventral element, and that the antero-medial element has become merged with the periventricular group of cells, probably forming a part of what has been termed by some the nucleus submedius.

The antero-dorsal nucleus in its well-developed form is distinguished by the large size of its cells. It cannot be certainly identified in some primitive and generalized mammals (e.g., Erinaceus), and in some forms it may reach an unusual size and definition (Macroscelides and rodents). In higher mammals it shows an increasing tendency to disappear, and in the higher primates is only a narrow band of cells capping the antero-ventral nucleus and sometimes grouped for description among the "nuclei disseminati." In most mammals the antero-dorsal nuclei of the two sides are interconnected by a well-marked commissure, the commissura inter-antero-dorsalis. The fibres of this commissure are well myelinated in lower mammals, but become unmyelinated in many of the higher types (e.g., carnivora [54]). The antero-dorsal nucleus has no representative in the reptilian thalamus.

The antero-ventral nucleus in higher mammals assumes a well-defined spherical form, clearly circumscribed by a medullary "capsule." It is termed the "anterior nucleus" in human descriptive anatomy and is responsible for the elevation of a rounded tubercle on the upper surface of the thalamus, the anterior tubercle. It is worthy of note that in many mammals an analogous tubercle is to be found in the same position, which is formed however by the rostral part of the lateral nucleus.

There has been some doubt regarding the relation of these elements of the anterior group of nuclei to the mammillo-thalamic tract. It is generally conceded that the fibres of this tract certainly end in the antero-ventral and antero-medial nuclei. Cajal described such a connection also for the antero-dorsal nucleus, but this has been more recently questioned. Such a connection is obvious, however, in Macroscelides in which the antero-dorsal element is relatively enormous, and Glorieux [22] has lately traced the termination of the mammillo-thalamic tract by Marchi degeneration into all the elements. This I have also established by my own experiments on rats [12]; in three cases in which the tract was sectioned on one side the degenerated fibres could be followed without

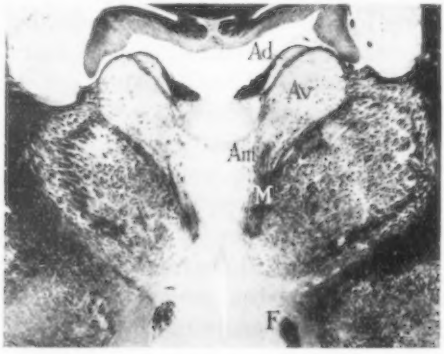

FIG. 5.—Section through the anterior group of nuclei of the thalamus of *Lemur Catta*. *Ad.* Nucleus antero-dorsalis. *Am.* Nucleus antero-medialis. *Av.* Nucleus antero-ventralis. *F.* Fornix. *M.* Mammillo-thalamic tract (Bundle of Vicq d'Azyr).

difficulty into the antero-medial, antero-ventral and antero-dorsal nuclei on the same side. I found also that some of the fibres enter the inter-antero-dorsal commissure and, crossing over the mid-line, enter the antero-dorsal nucleus of the opposite side. This corresponds with the appearance seen in Weigert sections of normal material in Macroscelides. In these experiments descending degeneration was always found after a lesion involving the bundle of Vicq d'Azyr, which could be traced readily into the medial nucleus of the ipsilateral mammillary body. It seems probable, therefore, that Edinger's contention that this bundle also contains thalamo-mammillary fibres is correct, at least in the rat. As regards internuclear connections, the three elements of the anterior group of nuclei are intimately related to each other by short medullated fibres. According to Rioch, the antero-ventral nucleus receives fibres

from the dorso-medial nucleus, the lateral nucleus, the rostral end of the ventral nucleus and the nucleus centralis. The antero-medial nucleus is closely connected with the nuclei of the midline and thus is brought into relation with the periventricular system, of which, indeed, it is to be regarded as a differentiated part.

The extra-thalamic connections of the anterior nuclei still require further study. The antero-medial nucleus of primitive mammalian brains probably is not related directly to the thalamic radiations, it is essentially a part of the "palæothalamus." Thalamic radiations, on the other hand, can be traced into the antero-ventral and antero-dorsal elements in normal Weigert preparations.

The question arises as to whether these fibres are cortical in their origin or destination. As I indicated in my previous paper, there is evidence of an experimental and comparative anatomical nature to suggest that at least a part of the anterior nuclear group is in direct communication with the cerebral cortex, and most probably with the cingular areas. On the other hand, Sachs [55] has stated categorically that none of the fibres issuing from the antero-ventral nucleus in the cat (his nucleus dorsalis magnus) pass beyond the caudate nucleus. This was also described by Glorieux as the result of his experimental work on the dog's thalamus. I have recently observed in Marchi preparations of the rat's brain that lesions involving the area cingularis of the cortex (either in its anterior or its posterior part) are followed by the appearance of fine Marchi granules in the fasciculi of the thalamic radiations which permeate the antero-ventral nucleus, but no degeneration is found in the other elements of the group. Conversely, a lesion involving the antero-ventral nucleus leads to Marchi degeneration in the radial fibres which penetrate into the area cingularis of the cortex along the whole extent of the corpus callosum. Lesions of the frontal pole were not followed by changes in the anterior nuclei. From these data it seems justifiable to infer that the antero-ventral nucleus in the rat is related by projection fibres to the cingular cortex,[1] and it seems improbable that it has any direct relation to the frontal lobe, except in so far as the area cingularis extends into the medial surface of this lobe. The relation of the antero-dorsal nucleus to the cortex is not definitely proved; a study of normal Weigert preparations of insectivore

[1] Since this was written, Mr. R. H. Boggon and the author, working in collaboration, have succeeded in producing a localized electrolytic lesion in the antero-ventral nucleus of the cat with the use of the Clarke-Horsley stereotaxic apparatus. Marchi preparations show degenerated fibres extending into the whole length of the cingular gyrus.

brains suggests that such a connection does exist. The peculiar features of the thalamus and cortex of Macroscelides furthermore suggest that this element may be in special relation with the very granular type of cortex found in the retrosplenial area. At the moment, however, this is a matter of speculation. The functional significance of the anterior nucleus is obscure. It has been pointed out above (*vide supra* p. 416) that the mammillo-thalamic tract is evidently a specialized portion of the periventricular fibre system. Since this fibre system appears to be concerned with the linking up of visceral neural mechanism in the hypothalamus with the somatic sensory centres of the thalamus, it may be conjectured that a similar function is subserved by the mammillo-thalamic tract. The anterior nucleus is certainly a receptive centre for impulses relayed from the hypothalamus through the mammillary body, and since the latter contains the main terminal nucleus of the fornix column it may be assumed that the functions of the anterior nucleus are closely bound up with those of the hippocampal formation. This, however, does not bring us much nearer the solution of the problem, for the functional significance of the hippocampus is itself a matter of speculation. We may note that even if the hippocampus was developed primarily as an olfactory cortical mechanism of some sort, it has evidently taken on other functions during its phylogenetic history, for it is a comparatively well-developed structure in the microsmatic human brain and even in the brain of anosmatic mammals. That the anterior nucleus must certainly be a thalamic element of some significance in the human brain is indicated by its size and differentiation, as well as by the size and definition of the mammillo-thalamic tract of which it is the terminal station.

The Relation of the Optic Tract to the Diencephalon.

It is well known that the fibres of the optic tract terminate mainly in the lateral geniculate body and the anterior colliculus of the mid-brain. There are, however, other terminal nuclei which, although relatively small, appear to be consistently present in those mammalian forms in which they have been sought. The course of the optic tract in the mammalian brain is schematically shown in fig. 6.

Before the optic tract reaches the lateral geniculate body in its course upwards and backwards, it gives off two small accessory tracts. The anterior accessory tract consists of fibres which leave the main tract as it passes obliquely across the crus cerebri. They have been identified in Marchi preparations and are described by some authorities (e.g.,

Loepp [38]) as piercing the peduncular fibres eventually to reach the subthalamic nucleus of Luys. I have identified this tract in the rat's brain after enucleation of one eye, but I was not able to follow the degenerated fibres further than the superficial aspect of the crus. Cajal [5] described in this position in rodents a thin stratum of cells which he stated to receive optic fibres. The posterior accessory optic tract leaves the main tract as the latter lies in topographical relation with the medial geniculate body. It forms a fine strand which runs obliquely in a caudo-ventro-medial direction across the crus, and is often known

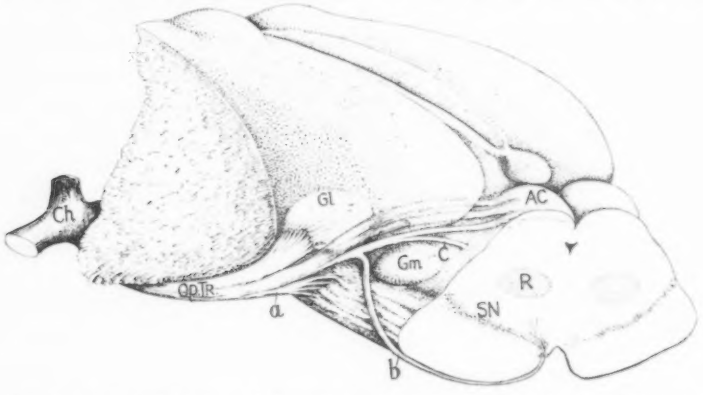

FIG. 6.—Terminal relations of the optic tract in the mammalian brain. *AC.* Anterior colliculus. *a.* Anterior accessory optic tract. *b.* Posterior accessory optic tract. *c.* Fibres passing to the large-celled nucleus of the optic tract. *Ch.* Optic chiasma. *Gl.* Lateral geniculate body. *Gm.* Medial geniculate body. *Op. Tr.* Optic tract. *R.* Red nucleus. *SN.* Substantia nigra.

as the tractus peduncularis transversus (see fig. 8). Its fibres end in the nucleus opticus tegmenti and the medial end of the substantia nigra, and some extend more dorsally into the tegmental region of the mid-brain [8]. For a discussion of these accessory tracts from the historical point of view, reference should be made to Tsai's paper on the optic tracts and centres in the opossum's brain [57].

Beyond the lateral geniculate body the optic tract passes into the stratum opticum of the anterior colliculus, many of its fibres penetrating the pulvinar to reach this destination, but the available evidence is against the commonly accepted statement that any retinal fibres end in the pulvinar. Weigert sections show that fibres of the mesencephalic root of the optic tract terminate in certain nuclear elements in the region of the tecto-thalamic junction; these are the large-celled nucleus of the optic tract and the pretectal nucleus. Experimental evidence

suggests that the fibres which enter the former nucleus are of retinal origin, while those which end in relation with the pretectal nucleus are probably derived from the lateral geniculate body (*vide infra*, p. 446).

Lateral Geniculate Body.

The morphology of the lateral geniculate body has been dealt with in some detail in a separate publication [11]. The main conclusions may be briefly summarized here. In a generalized and primitive mammal the lateral geniculate body may be divided into a ventral and a dorsal nucleus. The ventral nucleus is the more primitive element and receives collaterals from the crossed fibres of the optic tract. It is a differentiated lateral segment of the subthalamus and is connected with the zona incerta. The dorsal nucleus is a differentiated lateral part of the ventral nucleus of the thalamus, and in some insectivore brains the two are not sharply separated from each other. The dorsal nucleus is connected by fibre tracts with the ventral nucleus of the thalamus, the pulvinar, the tectum and the area striata of the cerebral cortex. In the primates, the ventral nucleus shrinks in size until it consists of a small collection of scattered cells lying among the entering fibres of the optic tract, the corpus pregeniculatum. The dorsal nucleus, on the other hand, becomes relatively large and laminated. There is some evidence to suggest that in the primary intrinsic differentiation of the nucleus three cell laminæ become defined. This trilaminar type later gives rise to a six-layered nucleus in association with the appearance of a hemi-decussation of fibres in the optic chiasma. Minkowski [41] originally suggested that the alternate laminæ in the Anthropoidea are associated with the termination of crossed and uncrossed fibres of the optic tract. I have adduced evidence in support of this contention in two cases (monkey and human material) in which unilateral optic atrophy had occurred some time before death. If the six layers of cells in the lateral geniculate body of these types are designated 1a, 1b, 2a, 2b, 3a and 3b from the superficial aspect, it may be definitely stated, as the result of these observations, that crossed fibres of the optic tract end in laminæ 1a, 2b, and 3b, while uncrossed fibres end in laminæ 1b, 2a, and 3a.

The Large-celled Nucleus of the Optic Tract.

If the optic tract is followed up on its course to the anterior colliculus in a primitive mammal in which the visual system is well

developed (e.g., Tupaia, Macroscelides), it will be found, after passing over the pars posterior of the lateral nucleus, to come into relation with a superficially placed group of cells which are distinguished by their large size. This is the large-celled nucleus of the optic tract and it corresponds to Cajal's [5] "noyau de la voie optique." It lies along the anterior and lateral margins of the anterior colliculus, and Weigert sections show many fibres penetrating into it from the optic tract, as was originally described by Cajal. It is not conclusively proved that these fibres are of retinal origin, as the Marchi method has not been employed in those animals in which the nucleus is conspicuously developed. I have found a few degenerated fibres of the optic tract extending into the topographical equivalent of the nucleus in the rat after excision of the eye [8] and a similar observation is recorded in the rabbit by Loepp [38], who designates the collection of cells as the nucleus parageniculatus. It seems probable, therefore, that the optic tract fibres which terminate in the large-celled nucleus of the optic tract have their origin in the retina.

The nucleus primitively occupies a superficial position between the tectum and the pars posterior of the lateral nucleus, lying over the pretectal nucleus. In small primates it can readily be recognized, but with the progressive growth and caudal displacement of the pulvinar it shows a tendency to sink from the surface and to be flattened out to form a plate of cells along the junctional plane of the pulvinar and the mid-brain. Along the line of this "infolding" numerous small branches of the posterior cerebral artery penetrate into the brain. In higher primates the nucleus loses its distinctive features and is apparently incorporated in the nucleus limitans which is taken as the boundary line between the thalamus and the mid-brain. The efferent connections of the nucleus are obscure. In Weigert sections fibres may be seen emerging from its medio-ventral aspect and passing into the deeper layers of the anterior colliculus. Cajal described the axis cylinders of the cells as losing themselves in the white substance of the tegmentum of the mid-brain. There is some reason for the suggestion, based upon topographical position and relation to the optic tract, that the large-celled nucleus is homologous with the nucleus lenticularis mesencephali of the reptilian brain.

The Pretectal Nucleus.

In the brains of small mammals an oval and often well circumscribed nucleus of small and medium-sized cells is situated immediately behind the upper end of the habenulo-peduncular tract, extending in a caudo-

ventral direction to the medial aspect of the medial geniculate body. It lies in amongst numerous fasciculi of tectothalamic fibres. This is the pretectal nucleus, and, like many other thalamic nuclei, it has been mentioned and described under a variety of names. Cajal described it in rodents as the posterior, the bigeminal, or the prebigeminal nucleus, and defined it as lying in front of the superior corpus quadrigeminum and above the posterior semilunar nucleus (which is the intralaminar nucleus bounding the ventral nucleus postero-superiorly). Above, it is in contact with the optic fibres destined for the superior corpus quadrigeminum, and below it prolongs itself towards the medial fillet. It will thus be observed that the nucleus lies close to the dorsal surface of the brain at the tecto-thalamic junction, and it may well be disputed whether the structure is to be relegated in descriptive anatomy to the mesencephalon or the diencephalon. Recent evidence suggests that the nucleus contributes corticipetal fibres to the posterior thalamic radiations and thus justifies its inclusion among the thalamic nuclei [46]. On the other hand Winkler states definitely that the pretectal nucleus undergoes no degenerative changes after cortical ablation affecting most of the hemisphere [62]. In lower primates (e.g., Microcebus [10], Lemur [47]) it becomes more sharply separated from the nuclear masses which lie ventro-laterally to it by the appearance of a nucleus limitans, the developmental formation of which is dealt with elsewhere (*vide supra*, 444). In the description of the primate thalamus, this nucleus limitans has usually been taken as the boundary between mesencephalon and diencephalon, so the pretectal nucleus has usually not been regarded as a thalamic nucleus. It may perhaps most conveniently be regarded as a junctional nucleus linking up the tectum with the thalamus, and its intermediate character functionally is certainly indicated by its rich fibre connections with both these structures as well as by the fact that it is traversed by tecto-thalamic fibres. Tsai [57] has described it in the opossum as the pretectal nucleus. Gurdjian [23] deals with it in the rat as the posterior nucleus, and it is included by some other authors (Rioch [52], Papez [45]) in the nucleus of the posterior commissure. In my study of the thalamus in the tree-shrew [6], I called it the posterior nucleus, following Gurdjian's nomenclature. Further studies showed me that it corresponds clearly with Cajal's prebigeminal nucleus (which term is clearly synonymous with the more convenient name pretectal nucleus), and that, moreover, the term posterior nucleus had been used by different authors for other entirely different nuclear masses. In my description of the thalamus of

Tarsius [7] and Microcebus [10], therefore, I have used the name pretectal nucleus.

The variations in relative size of the pretectal nucleus in different mammals is noteworthy. In the rat it is particularly well defined; in Macroscelides it reaches a relatively enormous size, and in transverse sections has an even and clear-cut circular contour; in the hedgehog it is not so large, and its outline is less definite, but it is very well differentiated cyto-architecturally. The significance of such variations is not clear, for they do not seem to be consistently related to other differences in the general structure of the brain.

Fibre connections.—The pretectal nucleus has numerous connections with neighbouring nuclei and is also traversed by many fibres of passage; of these tecto-thalamic and cortico-tectal fibres are the most conspicuous.

Cajal long ago described collaterals from the main part of the medial fillet as ending in the nucleus, and this relation has been confirmed by several observers since. It seems that, in some cases at least, the pretectal nucleus has been mistaken for the "medial nucleus" of the thalamus, though the latter lies anterior to the habenulo-peduncular tract, while the pretectal nucleus lies behind it. This error partly explains the current legend that the "medial nucleus" is the terminal for lemniscus fibres and the subsequent inference that the "medial nucleus" is the homologue of the nucleus rotundus of the reptilian brain. It is not known what particular component fibres of the medial lemniscus reach the pretectal nucleus.

It has been mentioned above that the pretectal nucleus is in intimate relation with the mesencephalic root of the optic tract. In Weigert sections made in an appropriate plane, fibres from the optic tract can readily be seen to penetrate the nucleus from its dorsal and lateral aspect. It seems very doubtful, however, whether these fibres are actually of retinal origin, for, after section of the optic nerve in the rat (in which the pretectal nucleus is particularly well developed), I have been able to trace only a few degenerated fibres from the optic tract as far as the lateral margin of the pretectal nucleus, but not into its substance [8]. These few fibres seem rather to end in relation to a collection of cells which represents the large-celled nucleus of the optic tract in this animal. If the optic connections of the pretectal nucleus are not of retinal origin, they are probably derived from the lateral geniculate body from which, in Weigert sections, many myelinated fibres can be seen to emerge to join the optic tract on its way towards the pretectal nucleus. This geniculo-pretectal tract, indeed, is well

figured, but not described by Cajal in his classical textbook. That the optic connections are by no means the most important afferent connections of the pretectal nucleus is indicated by the fact that the variations in the relative development of this nucleus in different mammals show no direct relation to the relative development of the visual apparatus.

Loepp [38], experimenting on rabbits, found that some retinal fibres of the optic tract terminated in a collection of cells lying between the medial geniculate body and the superior corpus quadrigeminum, which had been called by Lewandowsky the nucleus parageniculatus. From his figures and descriptions it seems fairly certain that these cells do not represent the nucleus pretectalis, but the large-celled nucleus of the optic tract, and in this case Loepp's findings coincide with my own observations in the rat.

In carnivores, Rioch found that the pretectal nucleus is connected directly with the tectum, the caudal pole of the dorso-medial nucleus, the posterior part of the lateral nucleus and the nucleus parafascicularis, besides receiving fibres from the brachium of the superior corpus quadrigeminum and the medial lemniscus. There is no doubt, indeed, that the nucleus is very closely interconnected with the superior corpus quadrigeminum, and also with the immediately adjacent thalamic nuclei, by short fibres, and Weigert preparations also indicate that it contributes fibres to the posterior commissure. Hines [28] has described the pretectal nucleus in the thalamus of the ornithorhynchus and finds it has connections with the tectum, habenula, dorsal part of the tegmentum, "medial" nucleus and the lateral geniculate body.

As regards efferent tracts of the pretectal nucleus, sagittal sections of small mammalian brains show a descending pretecto-tegmental tract which can be traced down to the tegmental region of the mid-brain immediately dorsal to the substantia nigra, and this tract I have found to be especially conspicuous and well defined in Erinaceus. Tsai [57] has indeed traced a tract of fibres actually to the substantia nigra itself and he terms it the tractus pretecto-nigralis.

The cortical connections of the nucleus are a matter of some interest. There can be little doubt that it receives cortico-pretectal fibres, for I have found in the rat that, after a local lesion in the posterior part of the parietal region, degenerated fibres can be traced up over the posterior surface of the ventral nucleus in fasciculi of the posterior thalamic radiations as far as the pretectal nucleus [12]. Papez believes he has demonstrated experimentally corticipetal connections in rats

after a lesion involving the nucleus; the degenerated fibres follow the same course as the corticifugal fibres, but Papez [46] was unable to state definitely in what area of the cortex they terminated.

Evolution of the pretectal nucleus.—It has been stated that in silver preparations the pretectal nucleus is seen to be filled with a mass of neuropil indicating diffuse interconnections with surrounding cell masses. This appearance is distinctly primitive and suggests an ancient phylogenetic history. In amphibia, Herrick has described a region which he calls the pars intercalaris diencephali occupying a relative position in regard to the tectum, posterior commissure, fasciculus retroflexus, optic tract, &c., almost precisely identical with that of the nucleus pretectalis in mammals, and he states that efferent fibres pass from it caudoventrally to the tegmental region of the mid-brain (area tegmentalis lateralis). Although no direct optic tract connections have been described for the pars intercalaris, it is, like the pretectal nucleus, crossed superficially by the mesencephalic root of this tract as it courses from the pars optica thalami (= lateral geniculate body of mammals) to the tectum, and there can be little doubt that the two must be, in part at least, homologous. In reptiles, the pars intercalaris has evidently undergone considerable differentiation, and at least four cell collections can be recognized in the pretectal area, the n. pretectalis, n. geniculato-pretectalis, n. lentiformis and n. spiriformis. The nucleus spiriformis is regarded by some authors as merely a differentiated part of the n. pretectalis. Of these cell masses in reptiles, it seems probable that the n. pretectalis, n. geniculo-pretectalis and n. spiriformis together represent the true equivalent of the mammalian pretectal nucleus. The n. geniculo-pretectalis receives collaterals from the optic tract (in Sphenodon according to Cairney [4]), while both it and the n. pretectalis are connected with the lateral geniculate body (Edinger [15], De Lange [36], Huber and Crosby [30]). They are intimately related to the substantia grisea of the tectum and are traversed by tecto-thalamic bundles. Moreover, from both these collections of cells a fasciculus pretectalis descendens has been described (Cairney [4] &c.), which certainly represents the pretecto-tegmental tract present in mammals. Crosby thinks it possible that strio-tectal fibres of the lateral fore-brain bundle connect with the pretectal nucleus of the alligator's thalamus.

If this provisional interpretation of homologies is correct, it appears that the pretectal region in reptiles shows a higher degree of intrinsic differentiation than in mammals. But this is perhaps only to be anticipated when it is recognized that the evolutionary history of the

brain is largely a matter of the gradual shifting forwards of centres of functional control from lower to higher levels. The diencephalic sensory correlation centres in the reptile are as yet simple in structure and relatively unelaborated and the differentiation of the pretectal region may be looked upon as a structural indication that the tectum is beginning to hand over its activities as a correlation centre to the thalamus. The pretectal nuclei in birds, from the description of Huber and Crosby [32], seem to be still more differentiated, no doubt in correlation with the high development of the visual sense. Owing to the ventral displacement of the optic lobes and the consequent distortion of adjacent topography, it is difficult to establish satisfactory homologies of the pretectal elements in the avian brain.

The pretectal nucleus among mammalia shows a considerable amount of variability, and it is still uncertain what the significance of this is. As far as I am aware, it is found among all members of this group, including the primates. With the growth of other elements it comes to form a relatively smaller proportion of the bulk of the thalamus as a whole, but in proportion to the size of the tectum it does not seem to undergo much change.

From a consideration of its terminal relation to the fibres of the optic tract, Tsai has suggested that the pretectal nucleus of the opossum may represent the phylogenetic origin of the pulvinar of the primate thalamus. This, however, is certainly not the case, for by a study of a series of brains representing as close an approximation as possible to a phylogenetic series I have been able to identify without difficulty the pretectal nucleus in lower primates in which a pulvinar is also present. Further, there is of course no evidence that medial fillet fibres end in the pulvinar as they certainly do in the pretectal nucleus.

Medial Geniculate Body.

In the brains of most primitive mammals the medial geniculate body forms a conspicuous tubercle at the caudal end of the lateral aspect of the thalamus. As is well-known, it receives a contribution from the lateral fillet, and it sends off the auditory radiations which are destined to terminate in the temporal region of the cerebral cortex. In most insectivore brains (e.g., Erinaceus, Sorex) the body is composed of cells of the same type as those which form the ventral nucleus of the thalamus, indeed the two are structurally continuous, so that it is impossible to define any boundary between them. This primitive condition seems to indicate that the medial geniculate body (as is the

case with the dorsal nucleus of the lateral geniculate body which represents an equivalent functional level) is a portion of the main sensory nucleus of the thalamus which has become secondarily differentiated in association with its auditory connections. In higher mammals, the medial geniculate body undergoes intrinsic differentiation. This is already to be observed in the progressive type of insectivore represented by Tupaia. In Tarsius, as in primates generally, it consists of a central mass of small cells in which the fibres of the lateral fillet appear mainly to terminate, caudo-ventrally there is a stratum of smaller cells which is related by fibre tracts to the zona incerta of the subthalamus, while dorso-laterally there is a larger-celled element which (as seen quite clearly in the brain of Tarsius) is derived from a caudal extension of the nucleus suprageniculatus, a part of the lateral group of nuclei (*vide infra*, p. 460). The caudo-ventral element, by analogy, is apparently the functional equivalent of the ventral nucleus of the lateral geniculate body, while the main central part of the medial geniculate body is the equivalent of the dorsal nucleus of the lateral geniculate body. The dorso-lateral element, it is suggested, bears the same relation to the main nucleus of the medial geniculate body that the pulvinar does to the lateral geniculate body. It contributes corticipetal fibres which join or form a part of the auditory radiations.

A study of the medial geniculate body in the mammalia indicates that its main part is a differentiated part of the ventral nucleus of the thalamus. This is not in accord with the generally accepted view that the nucleus isthmi of lower vertebrates is the precursor of the mammalian medial geniculate body. The nucleus isthmi of the reptilian brain certainly receives terminals of the lateral fillet system, and is connected with fibres of Gudden's supra-optic commissure (Kappers [35], Crosby [30]). It occupies, however, a very caudal position (lying caudal to the region of the posterior colliculus), and probably represents a mesencephalic element of the mammalian brain associated with the lateral fillet such as the nucleus of the lateral fillet, or perhaps the small-celled caudoventral element of the medial geniculate body.

In mammals, according to Rioch [54], only a proportion of the fibres of Gudden's commissure end in the medial geniculate body, the remainder continuing caudally, ventral to the medial geniculate body, to to some lower centre. Larsell [37] has described a nucleus isthmi in amphibia (the frog), but already in the primitive Necturus, Herrick [25] has traced fibres of the lateral lemniscus system right up to the main sensory nucleus of the thalamus (his pars dorsalis thalami) from which

the lower functional levels of the thalamus generally have been derived. It is probable indeed that the reptilian homologue of the main part of the medial geniculate body is also to be sought for in the thalamus itself, either in the caudal part of the nucleus dorso-lateralis anterior or the nucleus rotundus.

In mammals the medial geniculate body is connected by short fibres with the ventral nucleus of the thalamus and with the nucleus supra-geniculatus (Rioch [54], Glorieux [22]). In addition it is reciprocally connected with the temporal cortex. Monakow [43] (in the cat and man), Zacher [66], Mingazzini [40], Löwenstein [39] (in man), and Yoshida [65] (in the rabbit) found cell-degeneration in the medial geniculate body after lesions involving the temporal lobe of the cortex. Ferrier and Turner (quoted by Yoshida) followed Marchi degeneration into the superior temporal convolution of monkeys after a unilateral lesion involving the medial geniculate body. The medial geniculate body requires more detailed structural analysis. It seems certain that in some descriptive accounts elements have been assigned to it which do not rightly belong to it. Thus in Yoshida's paper, his dorsal nucleus of the medial geniculate body (which was left almost unaffected by lesions of the temporal cortex) is undoubtedly the caudal extremity of the pars posterior of the lateral nucleus or pulvinar, which at this level comes into close topographical relations with the medial geniculate body proper.

The Lateral Group of Nuclei.

The main part of the lateral nucleus.—One of the distinctive features of the thalamus of higher mammals when contrasted with lower forms is the relative expansion of its lateral nucleus which also undergoes an intrinsic differentiation into secondary nuclear masses which are not always easy to define with certainty.

In a schematic diagram of the thalamus of a simple and generalized type of mammalian thalamus (fig. 2) it will be seen that the transverse intralaminar nuclei formed by the n. paracentralis and the n. centralis lateralis roughly divide the thalamus into upper and lower moieties. While the latter is occupied largely by the fillet nucleus, the dorsal half of the thalamus contains among other elements the lateral nucleus. The main part of the lateral nucleus forms the gray matter at the dorsal surface of the thalamus, bounded medially by the dorso-medial nucleus and the medial medullary lamina, laterally by the reticular nucleus and ventrally by the ventral nucleus, and extending rostrally to

the lateral aspect of the anterior nuclear group (n. antero-dorsalis and n. antero-ventralis), and caudally to the posterior end of the thalamus at the level of the posterior commissure. In the simply constructed brain of a primitive primate, the boundaries of the lateral nucleus are fairly distinct. In rostral planes it is made up of a uniform collection of medium-sized and regularly arranged cells, relatively free of a matrix of myelinated fibres. In Weigert sections, therefore,it stands out as a somewhat light area. At its anterior extremity it is closely related to the anterior nucleus and in some forms (e.g., dog, cat, lemur) it is partly

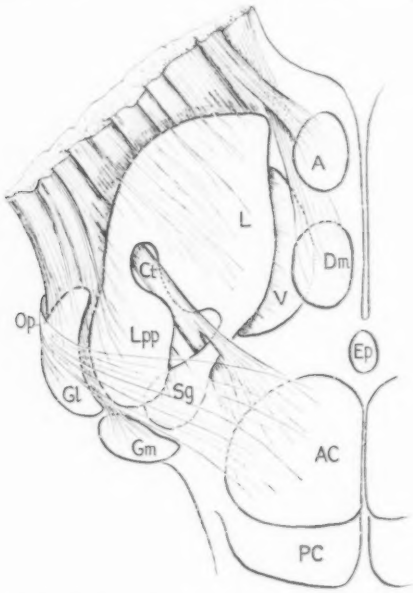

FIG. 7.—Schema of the thalamus to show the relations of the lateral nucleus and its extensions, viewed from the dorsal aspect. *A*. Anterior nucleus. *AC*. Anterior colliculus. *Ct*. Cortico-tectal tracts. *Dm*. Dorso-medial nucleus. *Ep*. Epiphysis. *Gl*. Lateral geniculate body. *Gm*. Medial geniculate body. *L*. Lateral nucleus, pars principalis. *Lpp*. Lateral nucleus, pars posterior. *Op*. Optic tract. *PC*. Posterior colliculus. *Sg*. Nucleus supragenicularus. *V*. Ventral nucleus.

responsible for an oval elevation on the front of the dorsal surface of the thalamus, the anterior tubercle. This part of the lateral nucleus I described in my accounts of the thalamus in Tupaia [6] and Tarsius [7] as nucleus lateralis *a*.

Traced caudally, the lateral nucleus expands transversely and also extends to a deeper plane as the ventral nucleus recedes from the

dorsal surface. Here the deeper part of the nucleus loses the regularity of its cytoarchitecture and it is penetrated by abundant fascicles of medullated fibres. This region may be termed nucleus lateralis *b*, though it must be emphasized that there is no sharp line of division between the *a* and *b* elements, at least on the basis of normal histological appearance. Towards the posterior end of the thalamus, the lateral nucleus appears to send off two conspicuous expansions, of which one is intimately associated with the lateral geniculate body and forms the pars posterior of the lateral nucleus, while the other is similarly related to the medial geniculate body and forms the nucleus suprageniculatus. Such is the condition in a primitive primate such as Tarsius, in which these elements of the lateral nucleus are particularly distinct and, indeed, serve almost as a schematic basis for the interpretation of the nucleus in mammalia generally. The subdivision of the main part of the lateral nucleus into a dorsal part "*la*" and a ventral part "*lb*," which I have distinguished in Tarsius, seems to correspond broadly with a similar division made by Friedemann [19] in the cercopithèque monkey, Winkler and Potter in the cat [64], and Pines [47] in lemur, but our knowledge of the nucleus as a whole is so meagre that it is not possible to do more than suggest such homologies tentatively. In general features, the deeper nucleus lateralis *b* exhibits transitional characters between n. lateralis *a* and the ventral nucleus, and in more elaborate brains it may be practically impossible to indicate any precise boundary line between the lateral and ventral nuclei, at any rate on the examination of normal preparations. It may be suggested that the separation of the lateral from the ventral nucleus is altogether arbitrary and artificial, and that it would be better to include these parts of the thalamus in one descriptive group, such as Burdach's external nucleus of the thalamus. But although along their contiguous margins these two nuclei may merge with each other, the lateral nucleus as described here forms a mass of grey matter extending over the dorsal surface of the thalamus which can not only be broadly distinguished from the ventral or fillet nucleus by a difference in cyto- and myeloarchitecture and its fibre connections, but also by the fact that it receives no fillet fibres. In simple non-primate brains the main part of the lateral nucleus is relatively a small thalamic element, considerably smaller, indeed, than its pars posterior. It does not extend so far rostrally relatively to the anterior nucleus, it does not reach so far back on the dorsal surface of the thalamus, and its transverse width is slight. This largely accounts for the fact that the thalamus in such

forms is more or less round in cross section, whereas in primate brains of an equivalent size the increase in width of the dorsal surface in conformity with the expansion of the lateral nucleus gives it more of a triangular section. Further, this expansion leads to a displacement of other nuclei, such as the external geniculate body, in a caudo-ventral direction.

Fibre connections of the lateral nucleus.—The fibre connections of the lateral nucleus are extraordinarily difficult to trace by the usual experimental methods, as it is traversed by so many fibres of passage, and it requires the greatest care to establish with certainty what fibres are actually interrupted here. From the study of normal Weigert sections of a variety of mammalian brains, there is no doubt that the main part of the lateral nucleus is in intimate fibre connection with the subjacent ventral nucleus and likewise with the other elements of the lateral nucleus, the pars posterior and the nucleus suprageniculatus. The connection with the ventral nucleus has been emphasized by Gurdjian [23] in the rat. This author also mentions connections with the superior thalamic radiations and, in its caudal part, with the tectum. In lower mammals the lateral nuclei of the two sides are linked together by commissural fibres which course through the intralaminar nucleus centralis lateralis. This commissural connection has been demonstrated experimentally in the dog by Glorieux [22]. Rostrally the lateral nucleus (n. lateralis *a*) is connected by internuclear fibres with the anterior nucleus, and especially with its antero-dorsal element. This is particularly obvious in an animal such as Macroscelides in which the antero-dorsal element attains a great development [9]. The relation between the two nuclei is also indicated by the fact that in some forms (e.g., Microcebus) the caudal part of the antero-dorsal nucleus is not clearly demarcated off from the anterior pole of the lateral nucleus as far as cytoarchitecture is concerned. Many fibres emerge from the medial aspect of the lateral nucleus to contribute to the medial medullary lamina and probably, through this, connect with the dorso-medial nucleus, n. parafascicularis (and the centre median nucleus), the pretectal nucleus and the tectum.

Rioch [54] made the following observations on the carnivore thalamus. His pars anterior (= n. lateralis *a*) connects with the anterior nucleus (especially the antero-dorsal element), the dorso-medial nucleus, and the pars intermedia of the lateral nucleus. The pars intermedia and pars posterior (= n. lateralis *b*) have internuclear connections with the dorso-medial nucleus, the ventral nucleus, the pulvinar and n. supra-

geniculatus, the n. parafascicularis and tectum. In addition, some parts are said to contribute to the superior and intermediate thalamic radiations.

Evidently von Monakow's nucleus antero-dorsalis corresponds to n. lateralis *a*, while his nucleus lateralis represents our n. lateralis *b*. Rioch, in his detailed study of the thalamus of carnivore, recognizes a pars anterior (= n. lateralis *a*), a pars intermedia and pars posterior (together representing n. lateralis *b*).

The cortical connections of the main part of the lateral nucleus are still uncertain in their details. Von Monakow [43], basing his evidence

FIG. 8.—Transverse section through the caudal part of the thalamus of the fruit bat (*Pteropus*). *AC*. Anterior colliculus. *FR*. Fasciculus retroflexus. *GLd*. Dorsal nucleus of lateral geniculate body. *Gm*. Medial geniculate body. *Lp*. Pars posterior of the lateral nucleus. *Npc*. Nucleus of the posterior commissure. *Nto*. Large-celled nucleus of the optic tract. *PC*. Posterior commissure. *Pr*. Pretectal nucleus. *PP*. Pes pedunculi. *Sg*. Nucleus suprageniculatus. *TO*. Optic tract. *TOa*. Posterior accessory optic tract. *V*. Posterior extremity of ventral nucleus.

on functional atrophy after cortical ablation, arrived at the conclusion that in mammals generally it is related to the parietal cortex, but that in man it is chiefly connected with the central convolutions. Minkowski [42] describes in the monkey corticipetal fibres from the anterior ex-

tremity of the dorso-lateral nucleus (= n. lateralis *a*) to the postero-superior part of the frontal region (superior frontal gyrus), from the middle third to the upper part of the precentral gyrus, from the posterior third to the upper part of the postcentral gyrus, and from the caudal extremity to the superior parietal lobule. He found no corticifugal fibres to the lateral nucleus.

Glorieux [22] concludes from his experiments on the dog that the cortical fibres of the lateral nucleus occupy the whole extent of the anterior limb of the internal capsule and are distributed to the anterior part of the parietal region anterior to the cruciate sulcus.

In regard to corticifugal fibres, Biemond [2] found evidence of these in the rabbit after cortical lesions of which one involved Brodmann's areas 17 and 29, a second areas 17, 29 and 22, and a third areas 7, 17, 18 and 29D. No degeneration was found in the lateral nucleus in this animal after an injury to the frontal region of the cortex. In the monkey, degeneration was present in the lateral nucleus after a lesion in the frontal region involving areas 6, 8, 4, 9, 10 and 11, but none was found after occipital lesions. In my own experiments on the rat's brain, a small lesion involving the most dorsal part of the parietal region of the cortex (just anterior to the area striata) led to Marchi degeneration in the main part of the lateral nucleus, and the result of thalamic lesions indicates that corticipetal fibres pass from the nucleus to the same region of the cortex. This cortical area, from its topographical position, is almost certainly the representative of the much more elaborate parietal association areas of higher mammals.

Minkowski's conclusions support the conception of von Monakow's school that the lateral thalamic nucleus is related to the "leg areas" of the central convolutions in the same way that the ventral nucleus is related to the "arm areas," but the facts that the lateral nucleus does not receive fillet fibres and that in higher mammals it expands out of all proportion to the size of the ventral nucleus, although in these forms there is no reason to suppose that the caudal half of the body requires a greatly increased representation in the thalamus or the Rolandic cortex, make it difficult to accept this interpretation.

On the whole, the evidence at hand suggests strongly that the lateral nucleus is mainly related to the parietal regions of the cortex, and this idea is supported by comparative anatomical evidence. A comparison of the brains of the tree-shrew (*Tupaia minor*) and the mouse lemur (*Microcebus murinus*) is especially instructive in this connection. They are readily comparable in size and general proportions, and a study of

their cortical lamination shows that the main sensory projection areas are of about the same extent in both. On the other hand, the "association areas" of the cortex, and especially the parietal and temporal regions, show a marked development in Microcebus as contrasted with Tupaia. In the thalamus, the ventral nucleus in both brains appears to be of much the same size, while the lateral nucleus in Microcebus is conspicuously developed in comparison with the same nucleus in the tree-shrew. It might be inferred from this that there is a functional relationship between the lateral nucleus and the "association areas" of the cortex, and, taking into account the fact that in Tupaia the medial geniculate body (related to the temporal area) is unusually small, it seems likely that the lateral nucleus is mainly related to the parietal cortex. This, indeed, is in harmony with the observation that throughout the mammalian series there is a close relation between the progressive elaboration of the lateral nucleus and the progressive expansion of the parietal region of the neopallium.

The Evolution and Functional Significance of the Lateral Nucleus.—The most striking feature of the main part of the lateral nucleus, from the comparative anatomical point of view, is its progressive enlargement and elaboration in the ascending mammalian scale. In primitive mammals, such as the common shrew (Sorex), it is extremely small, appearing at the dorsal surface of the thalamus immediately lateral to the anterior nucleus, but not apparent in caudal sections as a nuclear entity distinct from the ventral nucleus. In Erinaceus, the lateral nucleus is also small, and, judging from the figures in Tsai's paper [57], it is so in the Virginian opossum. In the tree-shrew [6], in which the brain has attained to a higher grade of development, the lateral nucleus is not only larger, but shows some degree of intrinsic differentiation. In the primitive primate, Microcebus (10), the lateral nucleus is larger, and in higher primates its increasing development is noteworthy. In these it is largely responsible for the great increase in the size of the thalamus and for the caudo-ventral displacement of some of the caudally situated nuclei such as the lateral geniculate body and the pars posterior of the lateral nucleus, and for the formation of a projecting posterior pole of the thalamus—the pulvinar. This increasing elaboration of the main part of the lateral nucleus certainly appears to run parallel with the progressive development of the so-called association areas of the cortex (especially if considered in comparison with the relatively more stationary ventral nucleus), and particularly with the parietal areas. This fact is suggestive of a direct functional relationship

between the main part of the lateral nucleus and the parietal cortex, and this, again, is supported to some extent by the study of fibre connections between these two parts of the brain.

The existence of a representative of the lateral thalamic nucleus in submammalian forms demands attention. If the main part of the lateral nucleus represents a higher functional level in the thalamus essentially associated with the more recently evolved regions of the neopallium, it will hardly be present as a distinct nucleus in the

FIG. 9.—Transverse section through the thalamus of the fruit bat (*Pteropus*) at the level of the upper end of the fasciculus retroflexus. *Ct.* Cortico-tectal tracts. *FR.* Fasciculus retroflexus. *GLd.* Dorsal nucleus of lateral geniculate body. *Glv.* Ventral nucleus of the lateral geniculate body. *Lp.* Pars posterior of the lateral nucleus. *PC.* Posterior commissure. *Pf.* Nucleus parafascicularis. *Pr.* Pretectal nucleus. *Pv.* Periventricular system. *PP.* Pes pedunculi. *TO.* Optic tract. *V.* Ventral nucleus.

sauropsidan brain. In Ornithorhynchus, the main part of the lateral nucleus is evidently represented by a part of the nucleus dorso-lateralis as described by Hines [28], and it is small and but feebly differentiated. In reptiles it is, in our interpretation, absent altogether, or at the most is represented by a few scattered cells at the dorso-lateral extremity of the nucleus dorso-lateralis anterior.

This conclusion necessarily follows from the discussion on the homologies of the ventral nucleus in the reptilian thalamus.

The lateral nucleus of the thalamus thus appears to be a mammalian character, only attaining to a conspicuous size and differentiation in those brains in which the "association areas" of the cortex begin to occupy an appreciable proportion of the neopallium.

From its close association with the subjacent ventral nucleus of the thalamus, it may be inferred that the main part of the lateral nucleus represents a higher intrathalamic functional level related principally to the sensory impulses which reach the ventral nucleus by the fillet. These impulses, having reached the ventral nucleus where they are represented in a relatively elementary form, may be there brought into relation with and modified by afferent impulses which come in from other thalamic nuclei of an equivalent functional level (e.g., the geniculate bodies and the anterior nucleus), and passed on to the main part of the lateral nucleus by short internuclear connections where they acquire a re-representation.

The pars posterior of the lateral nucleus.—In the thalamus of a primitive and generalized type of mammalian brain the main part of the lateral nucleus sends off two caudal extensions, the pars posterior of the lateral nucleus and the nucleus suprageniculatus. The pars posterior consists of the same type of cells as the main part of the lateral nucleus, and it extends caudo-ventrally immediately above and behind the dorsal nucleus of the lateral geniculate body, its close relation with which is one of its most distinctive features. It is intimately connected to it by internuclear fibres, and the two structures show a close parallel development in different mammalian forms. Caudally the pars posterior comes into topographical relation with the medial geniculate body and the anterior colliculus, superficially it is covered by mesencephalic fibres of the optic tract, many of which penetrate it on their way to the tectum, and it is separated from the main part of the lateral nucleus and from the lateral margin of the ventral nucleus by cortico-tectal fibres which help to form what has been termed the lateral medullary lamina of the thalamus. In mammalian brains, in which a relatively large anterior colliculus is combined with a high differentiation of the area striata of the cortex, these cortico-tectal fibres form a well-defined tract, so that the pars posterior of the lateral nucleus is sharply demarcated from deeper structures. It also receives fibres from the main part of the lateral nucleus, and, at its caudal extremity, from the tectum. There is no evidence that it receives

impulses directly from lower levels. From the pars posterior of the lateral nucleus, cortical projection fibres pass forwards in close association with the optic radiations which leave the lateral geniculate body, and, turning laterally into the internal capsule, they occupy here a position immediately in front of the geniculo-cortical fibres. So far as they can be followed in Weigert preparations of normal material, they are distributed to the cortex directly anterior to the area striata. This point has not been conclusively demonstrated by experimental study, as it is difficult to produce a lesion which is strictly localized to the pars posterior of the lateral nucleus without involving adjacent elements, but in one experiment in which the nucleus was involved by a thalamic lesion in a rat's brain [12] I was able to trace Marchi degeneration into the lower and anterior part of the area striata and into a narrow zone of cortex immediately in front of and below this area.

I have elsewhere [7] dealt with the evidence that the pars posterior of the lateral nucleus is the homologue of at least a part of what, in higher primates, is termed the pulvinar. It is unnecessary to repeat all this discussion here, but it may be noted that the pulvinar and the pars posterior of the lateral nucleus are identical in their topogaphical relations (as regards adjacent nuclei and fibre tracts), in their intra-thalamic connections, in their relation to the optic tract, and almost certainly in their cortical connections. The conclusion is reached that the thalamic element included in the term "pulvinar" is by no means a distinctive feature of the primate diencephalon. It is present and may even attain to a relatively large size in the brains of primitive mammals. A definite projecting pole at the caudal extremity of the thalamus to form a "pulvinar" is foreshadowed in Tarsius, and is dependent on the progressive increase in size of the main part of the lateral nucleus which leads to a displacement caudally of the pars posterior. Brouwer [3] has emphasized the fact that no retinal fibres terminate in the pulvinar, which is therefore not one of the primary optic centres of the brain. I can confirm this observation in the rat [8] as in this mammal, after section of the optic nerve, Marchi degeneration in the pars posterior is confined entirely to the fasciculi of the mesencephalic fibres of the optic tract which pass through it to reach the stratum opticum of the anterior colliculus, and there is no evidence that any of these fibres terminate in the nucleus.

Nucleus supragenículatus.—In the primitive primate, Tarsius, the caudal extensions of the lateral nucleus of the thalamus are particularly

easy to define. The pars posterior or pulvinar is clearly circumscribed by the relatively large cortico-tectal tracts; the other element, the nucleus suprageniculatus, is also sharply demarcated and can be readily traced by the differentiation of its cytoarchitecture as well as by the medullary laminæ which enclose it. It reaches in a caudo-ventro-lateral direction to the medial geniculate body, and ultimately can be traced as a continuous tract of cells into the dorso-lateral part of the medial

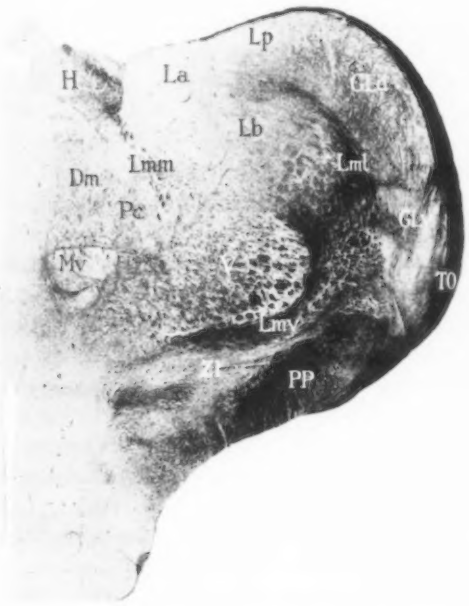

FIG. 10.—Transverse section through the middle of the thalamus of the fruit bat (*Pteropus*). *Dm.* Nucleus dorso-medialis. *GLd.* Dorsal nucleus of the lateral geniculate body. *GLv.* Ventral nucleus of the lateral geniculate body. *H.* Nucleus habenulæ. *La.* Pars principalis of the lateral nucleus, subdivision, *La.* *Lb.* Pars principalis of the lateral nucleus, subdivision. *Lb.* *Lml.* Lateral medullary lamina. *Lmm.* Medial medullary lamina. *Lmv.* Ventral medullary lamina. *Lp.* Pars posterior of the lateral nucleus. *Mv.* Nucleus medialis ventralis. *Pc.* Nucleus paracentralis. *PP.* Pes pedunculi. *TO.* Optic tract. *V.* Ventral nucleus. *ZI.* Zona incerta.

geniculate body with which it becomes incorporated. The nucleus suprageniculatus has been described and figured in the carnivore brain by Rioch [52], where it occupies a topographical position similar to that of Tarsius. It has also been described by Friedemann [19] in Cercopithecus. In the higher primates it is much less well defined and

its connections are difficult to make out. Rioch [54] mentions connections of the nucleus with the medial geniculate body, with the nucleus lateralis, with the tectum and with the medial medullary lamina. Fibres from it also run into the internal capsule in close association with the auditory radiations which spring from the main central part of the medial geniculate body. From a consideration of its relation to the main part of the lateral nucleus and its fibre connections it seems reasonable to suggest that the nucleus suprageniculatus has the same functional relation to the medial geniculate body that the pars posterior of the lateral nucleus has to the lateral geniculate body. This, however, is a question which demands further inquiry.

Centre Median Nucleus.

One of the most conspicuous and sharply defined elements of the human thalamus is the centre median nucleus of Luys. It occupies the caudal part of the thalamus, and reaches out in a dorso-lateral direction from near the mid-line between the dorso-medial nucleus above and the ventral nucleus below. Attempts to establish the homologies of the nucleus have resulted in discordant opinions, mainly because attention has not been given to phylogenetic considerations in the comparison of one brain with another. Its fibre connections also offer considerable difficulty, as it is penetrated by fibres of passage which run between the mid-brain and other parts of the thalamus.

The centre median nucleus is clearly distinguishable in the monkey [19] and the larger lemurs [47]. In the latter it is not so well circumscribed, and it merges caudally with the nucleus parafascicularis which encloses the upper part of the habenulo-peduncular tract. In Tarsius [7] it may also be recognized without difficulty; it occupies a relatively more dorsal position than in the higher primates, for in the latter the larger dorso-medial nucleus displaces it ventrally. In the small lemurs (e.g., *Microcebus murinus* and *Microcebus coquerelli*) the nucleus is less well defined and appears to be a rostro-lateral extension of the parafascicular nucleus. Still lower in the mammalian scale, in the tree-shew (*Tupaia minor*) [6] the nucleus is much less evident, but even here it can be detected as a small triangular mass of cells which appears as a feebly-marked differentiation of the caudal part of the paracentral nucleus, but which is not clearly demarcated from either the paracentral nucleus or the nucleus parafascicularis. A comparison of a graded series which approximates as closely as possible to a true phylogenetic series indicates, indeed, that the centre median nucleus

arises as a specialization of the caudal end of the paracentral nucleus, which is itself an interstitial nucleus lying in the medial medullary lamina. Thus in its primitive form the centre median nucleus is an intralaminar nucleus penetrated by fibres of the medial medullary lamina. As it develops it attains to the status of a principal nucleus which becomes encapsuled by medullary fibres. Weigert sections show that it is in intimate fibre relation with the medial medullary lamina, and through this is brought into relation mainly with the tectum behind and in front with the nuclear elements which make up the dorsal moiety of the thalamus. I have suggested that it may be regarded therefore as an integrating mechanism related to that part of the thalamus in which progressive differentiation and growth are most obtrusive in the higher primates, and that its great development in the human brain is explicable from this point of view. This interpretation is not in accord with other views which have been advanced on its significance. Recently, however, Rioch [53] has advanced evidence to support the thesis that the centre median nucleus belongs neither to the lateral nor the medial group of thalamic nuclei, but represents a local elaboration of the interstitial nucleus of the medial medullary lamina. It has been stated that it receives fillet fibres; this partly rests upon the experimental evidence of Wallenberg, who traced Marchi degeneration into the medial medullary lamina in the rabbit after lesions involving the trigeminal fillet, and suggested that this termination of the degenerated fibres in the rabbit is homologous with the centre median nucleus of higher primates. This is, however, open to question, and my own experiments on the rat indicate that, although some degenerated fibres can be traced into the medial medullary lamina after a lesion involving the fillet system, they appear to be fibres of passage on their way to the dorsal aspect of the ventral nucleus. Vogt described a slight Marchi degeneration extending into the centre median nucleus of the monkey after destruction of the posterior column nuclei; this requires corroboration and it is also necessary to exclude fibres of passage which penetrate the caudo-ventral part of the centre median nucleus. An examination of a fœtal human brain at the twenty-fourth week (for a study of which I am indebted to Professor Lucas Keane and Dr. Hewer), in which the medial fillet first begins to become myelinated, shows that fillet fibres course through the caudo-ventral part of the centre median nucleus, but at this stage the greater part of this nucleus is free of myelinated fibres. Whatever the significance of the centre median nucleus, its progressive development in the mammalian series, as shown by comparative

anatomical studies, indicates conclusively that it is far from being a primitive formation.

The Dorso-medial Nucleus.

Situated in the dorsal moiety of the thalamus above the level of the paracentral nucleus and close to the mid-line is a group of medium-sized cells which can be distinguished with little difficulty in most mammalian brains. This is the dorso-medial nucleus. It is bounded laterally by the medial medullary lamina, medially by the paraventricular nucleus, rostrally it extends forwards to the anterior nucleus, and caudally it is limited by the fasciculus retroflexus. Reference has already been made to this nucleus in discussing the ventral nucleus of the thalamus and its connections and homologies, and it was pointed out that, largely as the result of a confusion of nomenclature, the dorso-medial nucleus is often described as the terminal station of fibres of the trigeminal fillet, as the equivalent of the reptilian nucleus rotundus, and as a representative, therefore, of the phylogenetically more ancient part of the thalamus. The common description of the nucleus as a component of the "medial group" of thalamic nuclei which are often regarded as "palæothalamic centres" has, I think, added to a misconception of its true significance. The nucleus is the equivalent of v. Monakow's nucleus medialis *a*, of the nucleus medialis of human descriptive anatomy, and of the nucleus medialis dorsalis of many recent authors. The significance of the nucleus is indicated rather by its dorsal position—for it is developed essentially in relation to the upper levels of the thalamus—and it seems advisable to emphasize this fact by terming it the nucleus dorso-medialis.

A survey of a series of mammalian brains shows that in the more advanced types the dorso-medial nucleus becomes progressively larger, better defined and increasingly differentiated. In man, indeed, it seems to have attained the height of its development in these respects. In primitive mammals it consists of a few and scattered cells, and its limits are by no means clear cut. In higher types the constituent cells increase in number and become more compactly arranged. In the primates, an intrinsic differentiation is to be found, so that a medial large-celled and a lateral small-celled element can be distinguished. The differentiation can be made out on the basis of myeloarchitecture as well as on the basis of cytoarchitecture. This progressive elaboration of the dorso-medial nucleus in the mammalian scale is hardly consistent with the idea that the nucleus is a primitive thalamic element. It may be repeated here that no evidence has ever been adduced to suggest that it receives fillet fibres. Wallenberg's implication that in different mammals there

is a direct relation between the size of the dorso-medial nucleus and the development of the trigeminal system is due to an error of interpretation—his diagrams show that he is really referring to the pretectal nucleus (which lies *behind* the fasciculus retroflexus). Moreover, in Ornithorhynchus [28], in which the trigeminal nerve and its nuclei attain to prodigious proportions, there is no defined element in the thalamus which can be identified as the dorso-medial nucleus. In the interpretation adopted here (*vide supra* p. 434), the dorso-medial nucleus is not represented in the reptilian thalamus—it is essentially a mammalian structure.

The dorso-medial nucleus is intimately related to the fibres which course through the medial medullary lamina. Through these fibres it is probably brought into relation with all the neighbouring elements which form the dorsal levels of the thalamus, especially the lateral nucleus and the centre median nucleus. Its caudal extremity receives fibres which emanate from the nucleus parafascicularis and the deeper strata of the tectum. Horsley and Clarke [29] found fibres of the superior cerebellar peduncle ending in the "nucleus medius" in experimental animals. Rioch describes internuclear connections with the medial part of the ventral nucleus and with the periventricular system of fibres as well as with the nuclei of the mid-line (especially nucleus rhomboidalis). These periventricular connections, according to this author (whose observations are based on the examination of normal Weigert material), connect the dorso-medial nucleus with the nucleus hypothalamicus posterior, the nucleus supramammillaris and the tegmentum. I have been able to follow degenerated fibres into the periventricular system as the result of a small localized lesion involving the dorso-medial nucleus in the rat, though I was not able to trace them as far as the hypothalamus. Nevertheless, the intimate connection between the dorso-medial nucleus and the periventricular system and the nuclei of the mid-line is an important fact, and there can be little doubt that through this system the nucleus can be brought into direct functional relation with the activities of the hypothalamus. Sachs [55] found degenerated fibres in the centre median nucleus after a lesion involving the "medial nucleus" (which is probably the equivalent of the dorso-medial nucleus), and he traced efferent fibres also from the medial nucleus to the caudate nucleus and probably to the lateral nucleus of the thalamus. He maintained, however, that it had no cortical connections. It is, however, well established that the dorso-medial nucleus receives components from the thalamic radiations,

most of which run up in a dorsal and medial direction from the inner part of the internal capsule through the ventral nucleus to reach the ventro-lateral aspect of the dorso-medial nucleus. The question arises as to whether these fibres are of cortical origin. V. Monakow [43] postulated a fibre connection between the "medial" nucleus and the frontal convolutions in man. Dejerine [14] reported a case in which a lesion of the frontal lobe was followed by degeneration of the anterior part of the "medial" nucleus. Minkowski [42] describes in the monkey corticipetal fibres from nucleus medialis *a* (dorso-medial nucleus) to an extensive area of the frontal region, reaching forward to the frontal pole. He does not mention any corticifugal fibres related to this nucleus in his experimental studies of corticothalamic connections. Riese [51] found in the dog that a lesion of the precentral region led to a fine Marchi degeneration in the region of nucleus medialis *a*, and nucleus medialis *b*, and he quotes C. and O. Vogt as accepting a corticothalamic connection from the precentral cortex to nucleus medialis *a*. Biemond [2] describes degenerated fibres ending in the nucleus medialis thalami after a lesion in the frontal lobes of the rabbit (involving Brodmann's areas 4, 3 and 1). In my own experiments on the rat's brain I found that lesions of the frontal pole of the cerebrum gave rise to degenerated fibres which could be traced in continuity into the dorso-medial nucleus, and, conversely, lesions of the dorso-medial nucleus are followed by Marchi degeneration in fibres which can be traced in the reverse direction to the frontal pole. These fibres occupy the most medial fasciculi of the internal capsule, and course forwards in close topographical relation to the septal region near the medial surface of the hemisphere. There is abundant reason to believe, therefore, that there exists a direct fibre relation between the dorso-medial nucleus and the frontal cortical areas, and it is a matter of some significance that in the mammalian series there appears to be a close parallel between the progressive development of the prefrontal areas of the cortex and progressive elaboration of the dorso-medial nucleus. Such a relation further strengthens the opinion that the dorso-medial nucleus is not represented by any nuclear homologue in the sub-mammalian thalamus.

The functional importance of the dorso-medial nucleus would seem to depend very largely upon its connections with the frontal lobe of the cerebral hemisphere on the one hand and with the periventricular system on the other hand. The periventricular system, as already indicated, consists of median collections of nerve-cells (nucleus reuniens,

nucleus rhomboidalis, &c.) forming the basis of the massa intermedia of the third ventricle, and of fine medullated and non-medullated fibres which run in a subependymal position among the cells. The system links up the pars dorsalis with the pars ventralis diencephali. In dealing with the evolutionary history of this part of the brain and with the connections of the hypothalamus, reference was made to the contrasting rôles which are apparently played by the dorsal and ventral parts of the diencephalon in the psychic life of the organism. The hypothalamus, it was noted, is kept in close touch with all those visceral activities which comprise the vegetative functions of the body, and it is able to do this in virtue of its nervous connections and of its relations to the pituitary gland. It seems to be an essential element in the integration of emotional reactions and in the psychogenesis of emotional experience. While the ventral part of the diencephalon is thus essentially concerned with the internal environment of the organism, the dorsal part (which includes the thalamus proper and the epithalamus) forms an elaborate sensory correlation centre for the reception of impulses which owe their origin to changes in the external environment. It is through the pars dorsalis diencephali that the organism is enabled to develop an awareness of objective phenomena. Thus the two parts of the diencephalon seem to be primarily concerned with two contrasting aspects of conscious activity, and, as we have seen, even in the earliest type of vertebrate brain it is possible to discern in a primitive and simplified form the structural basis of this dualism of psychic life. The periventricular system of fibres and interstitial nuclei may perhaps be regarded fundamentally as a link between the dorsal and ventral parts of the diencephalon, an anatomical connection through which external stimuli may be appropriately articulated with the organic functions of the body at the diencephalic level.

If the dorso-medial nucleus is regarded in the light of these considerations, it will be realized that it occupies a significant position, forming as it does an intermediate station through which the whole periventricular system can be brought under the dominating influence of the frontal cortex of the cerebral hemisphere. In other words, the dorso-medial nucleus provides a mechanism whereby the highest functional levels of the brain are enabled to control the more primitive elements of mental activity, such as are represented in emotional reactions, instinctive impulses, &c. In this connection reference may be made to the experiments of Fulton and Ingraham [21], who, by making an incision in the prechiasmatic region of the medial surface

of the cerebral hemisphere of cats, were able to alter profoundly the emotional behaviour of the animals. It is probable that this lesion involved the course of the fibres which run from the frontal pole back to the dorso-medial nucleus of the thalamus. It is possible also, on anatomical grounds, for corticipetal impulses to reach the prefrontal areas of the cortex along the same system, so that in these areas the resultants of all the diverse activities of the cerebral cortex may be brought into close functional relation with the activities of the visceral centres of the hypothalamus. The prefrontal areas may thus be regarded as a final product of cerebral development where the activities of the purely cortical mechanisms underlying the intellectual components of personality are equated with the activities of the hypothalamic region which are associated with the more fundamental and primitive components. In this way a means is provided for harnessing the impulses which are indissolubly linked up with elementary forms of emotional experience to the intentions and resolves which have their origin in ideational processes taking place at the highest intellectual levels.

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Notices of Recent Publications.

Brain and Spinal Cord: A Manual for the Study of the Morphology and Fibre Tracts of the Central Nervous System. By Emil Villiger. Edited by W. H. F. Addison. Fourth revised American Edition from the eighth to tenth German Edition. Pp. 337. J. P. Lippincott Company, Philadelphia and London. 1931. Price 25s.

It is always a pleasure to welcome a new edition of this valuable laboratory handbook, although the present edition contains few alterations from that of 1925. In the text more up-to-date descriptions of the neuroglia and of the connections of the basal ganglia are given, and several new diagrams and drawings are substituted for those in earlier editions. These changes are all for the better and it is especially pleasing to see that a good drawing of the circle of Willis has been introduced. The absence of any description of the vascular supply of the brain from almost all monographs on the anatomy of the nervous system is all the more regrettable since the descriptions given in the larger textbooks of anatomy are in most cases incomplete and even misleading. The illustrations of sections through the brain-stem make this book so valuable to the student of neurology that we should like to see it still further adapted to his needs by amplification of the sections devoted to those parts which have most clinical interest. For example, only eighteen lines are devoted to the basal ganglia and no description is given of their cell structure, although an excellent new diagram illustrates their connections. When we contrast this with the twenty pages devoted to the rhinencephalon we see the wide gulf which still separates the anatomist's point of view from that of the neurologist. We should also like to see more attention devoted to the main efferent and afferent tracts uniting the brain with the spinal cord. For example, the student is left to guess the position of the spinothalamic tract in the brain-stem; there is nothing either in the letterpress or the illustrations to help him. These may appear small omissions, but they detract seriously from the value of the book to the students of neurology for whom it is intended.

Anatomie des Menschen. von Hermann Braus. Band III. Centrales Nervensystem. von Curt Elze. Berlin: Julius Springer. 1932. S. 234. Price Rm. 14.80.

Professor Curt has produced a well-balanced and lucidly written account of the gross and minute anatomy of the brain and spinal cord. The illustrations are new, abundant and for the most part excellent. Minor defects are that the account of the glia does not embody the most recent work, and that some of

the coloured diagrams of the main projection pathways are not as clear as is desirable, clarity having been sacrificed to aesthetic considerations.

A more serious objection is the inclusion of sections dealing with physiology. They are too brief to do justice to the subject, and they are in many instances not acceptable in point of accuracy. Thus the sensory cortex is divided into "centres" that are supposed to be concerned in different aspects of sensory perception; there are frequent references to the central pathways concerned with "protopathic sensibility," and an account of the speech functions that is highly conventional and artificial.

Nevertheless, if the reader will pass over these irrelevant sections, he will find a concise and readable description of the morphology of the central nervous system.

Humoral Agents in Nervous Activity. By G. H. Parker. Pp. 79. Cambridge University Press. 1932. Price 6s.

In one of the most interesting and suggestive books on the nervous system that has appeared for some time, Dr. Parker presents a series of observations that argue in favour of a secretory activity of the nervous system. Except in a few lowly organized examples the evidence in favour of such activity is purely hypothetical, but many other phenomena and experiments discussed here bring it at least within the bounds of possibility that secretion may play a part in more complex nervous processes, possibly even in mental operations. The most definite facts have been obtained by the investigation of the chromatophores, the organs by which changes in colour can be effected: it has been found that in certain classes these are controlled by nervous, in others, by humoral influences, while in some both nervous and humoral influences play a part. There is also evidence that the nerves which act on the heart do so through secreted substances, and other muscles may be excited to activity by similar humoral substances, probably produced at the nerve terminals. The receptors may act in much the same way, an effective stimulus producing a chemical substance capable of exciting nerve-fibres. The author admits that many of his suggestions are purely hypothetical, but they present a new point of view in the investigation of nervous problems.

Intracranial Suppuration. By Miles Atkinson. London: Jonathan Cape. 1932. Pp. 124. Price 5s.

This little monograph is offered as a guide to the general practitioner in the recognition of intracranial suppuration, and in effect may be said to deal mainly with the intracranial complications of middle-ear disease.

The pathology of the condition is clearly and briefly discussed, and there are useful chapters on the prevention of intracranial complications and on their early recognition. Perhaps the weakest feature of the book is its clinical descriptions of intracranial abscess, particularly where localizing signs are concerned. It is true that the author maintains that localizing signs are

virtually terminal phenomena, may even be absent throughout the clinical course, and that once an abscess is suspected exploratory puncture should be performed. But his account of the localizing signs characteristic of frontal, temporo-sphenoidal and cerebellar abscess is so inadequate that the reader could not possibly make a localizing diagnosis on the information provided. Thus, in the case of frontal abscess he states that while "altered disposition, moral perversion, &c.," might be expected, they do not in fact occur, and that paresis of the crossed arm is a sign to be relied on, though it may equally occur with temporo-sphenoidal abscess. His accounts of temporo-sphenoidal and cerebellar abscess are a little more satisfying.

In the circumstances it may not be surprising that the author does rely upon localizing signs. The remedy for this, however, is not random puncturing of the brain, but the study at the bedside of the signs and symptoms of focal brain lesions. The author may be assured that by this means an intracranial abscess may be localized much earlier in its history than he supposes. By reason of its defects in this respect, the book loses much of the usefulness it might otherwise have.

Maladies du Système nerveux. Par HENRI CLAUDE. Two Volumes. 2e edition. Pp. 1,568. Paris: J. B. Baillière et fils. 1932.

The second edition of this textbook has been carefully brought up to date and expanded to meet the need of the student and the practitioner. It is still characterized by direct and lucid descriptions of the symptoms of disease and by its comprehensiveness despite its relatively small bulk. It is a pity it is not more liberally illustrated and that the paper on which they are printed does not show up satisfactorily many of the pictures provided. The lack of references deprives these volumes of much of the value they would otherwise have, but they will undoubtedly be widely consulted as the presentation of the personal views of a distinguished French neurologist. There is a useful index.

Les Tumeurs du Quatrième Ventricule. Par J. LEREBOULLET. Pp. 431. Paris: J. B. Baillière et fils. 1932. Price 65 francs.

The relative frequency of growths occupying or projecting into the fourth ventricle makes this monograph a valuable addition to the literature on cerebral tumours. It is based on twenty cases hitherto unpublished which were personally studied and an analysis of 320 cases collected from the literature. After a short review of the anatomy and embryology of this region the author describes the chief symptoms produced by these tumours and their value in diagnosis and localization; he lays weight on the prominence of general pressure disturbances, the occurrence of tonic seizures of the type described by Jackson, and the tendency for the cranial nerves to escape. Abnormal attitudes of the head and hypo-excitability of the labyrinths are also regarded as symptoms of value in diagnosis. The clinical and histological features of the various types of tumour found in the fourth ventricle are

then described at length; in these chapters there is an unnecessary recapitulation of symptoms discussed earlier, and the sections on histology might have been abbreviated as the author has nothing to add on the classification or nature of these growths.

Handbuch der Geisteskrankheiten. Herausgegeben von OSWALD BUMKE. Band 11, Spez. Teil VII. S. 1,132, mit 645 zum Teil farbigen Abbildungen. Berlin: Julius Springer. 1930. Price 187·60 Rm. (mit Notnachlass Rm. 169.84).

This large and magnificent volume presents a complete picture of what is known concerning the anatomical changes in the psychoses. It is edited by Professor W. Spielmeyer, whose introduction to the book is a clearly conceived and masterly disquisition on the place and value of anatomical study in relation to mental disorders. He emphasizes that histopathological studies are here ancillary to the clinical problems of psychiatry. He deals first with the qualitative analysis of the anatomical findings and their localization; and he discusses the making of an anatomical diagnosis, the pathogenetic analysis and physiological interpretation of the findings and their application to the question of symptomatology, course and treatment as well as to the general biological aspects of the whole problem. In this last section the sobriety of Spielmeyer's wide and critical survey is especially evident.

W. Weimann writes on intoxications, including such endogenous ones as may be associated with diseases of the blood and endocrine glands. He is also responsible for the section on infections. Spatz has an exhaustive monograph on encephalitis of every kind; the distinctions between true and pseudo-encephalitis are carefully examined and the clinical significance of the anatomical findings in epidemic encephalitis set forth. Steiner writes a restrained chapter on disseminated sclerosis and Schilder's disease, which is followed by one on cerebral trauma by Neubürger and v. Braunmühl. A most comprehensive account of the changes that may be effected by syphilis in the brain occupies the next 200 pages, Franz Jahnel writing on general paralysis, and the late Professor Jakob on syphilis of the brain and its membranes. Arterio-sclerosis by K. Neubürger, senile dementia and Alzheimer's disease by E. Grunthal, and Pick's disease by v. Braunmuhl, are sections in which the clinical relations are constantly borne in mind. Epilepsy is dealt with by W. Scholz, and dementia præcox briefly by H. Josephy. Schob writes a most thorough and authoritative monograph on the various conditions that may be associated with idiocy. The volume concludes with two articles by J. Hallervorden, one on extra-pyramidal disorders and the other, of notable value, on the various processes which cannot properly be included in any of the familiar categories.

This is not so much a book as a collection of monographs of the first order. Its general production and appearance is beyond cavil: this is particularly true of the excellent microphotographs and other illustrations. The indices and bibliographical lists are exhaustive.

L'Intuition délirante. Par R. Targowla et J. Dublineau. Paris: Maloine. 1931. Pp. 316. Price 35 fr.

This memoir is an amplified version of a paper by Dr. Dublineau which won the Prix Esquirol in 1929. It is concerned with delusional ideas which rise suddenly into consciousness, are accompanied by a feeling of immediate and absolute certainty beyond all proof or disproof, and are entirely personal. The authors do not attempt psychological analysis of this symptom but only its clinical description and study. This little book shows very well the dangers as well as the value of purely descriptive work, of which the result is commonly to make independent and significant that which is merely a particular aspect of a general psychic disturbance, to introduce fresh categories, and to present in a new light not always brighter than the old one. The discussion of intuition in general by the authors and their clinical analysis will be found informative.

La Folie au XXe Siècle. Par A. Rodiet et G. Heuyer. Paris: Masson. 1931. Pp. 359. Price 40 fr.

In order to ascertain whether since the war there has been in France, and particularly in Paris, a change in the incidence and forms of mental disorder the authors have examined the records of the special infirmary which serves as a clearing house for the majority of the insane of Paris. In the event, however, the work in which this is reported becomes a textbook of French psychiatry with illustrative case histories. The third part of the book deals with the various modes of disposal and treatment, largely from the point of view of the administrator. To the question the writers set out to investigate they give a negative answer.

Psychological Factors in Peripheral Vision. By G. C. Grindley. Medical Research Council Report. No. 163. London: 1931. Pp. 49. Price 1s.

Studies of the kind here described are not easily to be interpreted as yet but they furnish interesting provisional data which will doubtless contribute to the working out of the theory of perception. The author is well aware of the artificial nature of his experiments, which were concerned with the tachistoscopic exposure of various forms in the peripheral field; he draws no premature conclusions but is content to state the findings and suggest caution. He is inclined to the view that the central factors involved in peripheral form perception are not radically different from those operating in direct vision. It does not appear from the list of references that the author is acquainted at first hand with the excellent studies of the Leipzig school (Krueger, Sander, Schneider) which bear closely upon his research.

Il Processo Fine della Coscienza. By CASIMIRO FRANK. Roma: Tipografia La Precisa. 1931. Pp. 386. Price L. 50.

Like many other writers of large and ambitious books in this branch of medicine, Dr. Frank invents new words and makes extreme claims. He attempts to bring his psychological views into relation with the known structural arrangements in the cerebral cortex, but the attempted synthesis is unhappy, and the psychological views put forward will not find general acceptance. The author attributes great importance to suggestibility in normal as in morbid psychology, or as he calls it "biopsychology," and on this he bases his "biopsychotherapy" and "biopsychagogia," in which the chief work is done by "corticagogia," a verbal procedure. The author's earlier study of speech-disorders during the war has here influenced him a good deal.

Psychopathology of Forced Movements and the Oculogyric Crises of Lethargic Encephalitis. By SMITH ELY JELLIFFE. Nervous and Mental Disease Publishing Co., New York and Washington. 1932. Pp. 219. Price $4.00.

The first half of this book is devoted to an exhaustive account of the literature of oculogyric crises. Jelliffe then reports briefly his own four cases, two of whom have been described in his earlier work on postencephalitic respiratory disorders, and passes to the psychoanalytical interpretation of the symptoms. The polemical and omnium gatherum style of this part of the monograph makes it unusually difficult to do justice to the author's attempt at explanation in terms of psychological and biological happenings. If one can accept the Freudian method of approach as being applicable to such phenomena as these, the material presented is interesting, but it is in any case associated with a rather inchoate mass of allusions to names and scientific catch-phrases. It is unfortunate that where such wide reading has gone to the making of a book it should appear to be so ill-digested.

Zur Klinik und Analyse der psychomotorischen Störung. von OTTO KAUDERS. Berlin: S. Karger. 1931. S. 132. Price Rm. 12.60.

The chief value of this phenomenological study of the motor disturbances in mental disorder lies in the protocols and the detailed, if wordy, discussion of motor processes as manifestations of the total personality. The investigation, which was largely concerned with delirious patients, showed how futile is the assumption that purely neurological or purely psychopathological explanations are adequate in this field. Although the writer has brought in more or less relevant anthropological and biological matters, the treatment is too heavy for the slender material; there is nothing particularly new or stimulating in it.

Neurobiologie de l'Hallucination. Essai sur une variété particulière de désintégration de la fonction. Par RAOUL MOURGUE. Bruxelles: Maurice Lamertin. 1932. Pp. 416. Price 65 fr.

Dr. Mourgue has been studying the problem of hallucinations for the last fifteen years; in that time he has read an incredible number of articles and books, here listed, most of which he found unhelpful, and worked out a hypothesis for which he claims a pragmatic value, equivalent to truth. The hypothesis is based on the general biological theory propounded by himself and the late Professor v. Monakow, and there is also great indebtedness to the teaching of M. Bergson, who writes an appreciative preface to the book.

The author rejects entirely the familiar notion that hallucinations are intensified and exteriorized images, and concludes that they represent a special form of the interaction of the two spheres, of instinct and orientation. It is especially with the spatial and motor aspects of hallucination that he is concerned. Normal perception and many related problems of psychology are drawn into the argument. The work is coherent, clear, and makes no extravagant claims: it is a distinguished accession to the very few comprehensive works on this subject.

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EDITOR.